

Titania-Supported Iridium Subnanoclusters as an Efficient Heterogeneous Catalyst for Direct Synthesis of Quinolines from Nitroarenes and Aliphatic Alcohols**

Lin He, Jian-Qiang Wang, Ya Gong, Yong-Mei Liu, Yong Cao,* He-Yong He, and Kang-Nian Fan

Dedicated to the Fritz Haber Institute, Berlin, on the occasion of its 100th anniversary

The use of metal nanoparticles (NPs) or nanoclusters (NCs) as versatile catalysts for green and sustainable organic synthesis has attracted tremendous interest in recent years owing to their unique properties, such as a large surface-to-volume ratio and tunable shapes.^[1] The control of their size, shape, dispersity, and in particular the combination of metal NPs/NCs with a specific heterogeneous support is essential for enhanced activity and selectivity in a desired application.^[2] Although in many classical transformations, reusable supported metal NPs/NCs have exhibited far superior performance than those of conventional metal complex catalysts,^[3] the possibilities offered by metal NPs/NCs for sustainable tandem catalysis that allows a rapid increase in molecular complexity through one-pot multistep reactions have scarcely been explored.^[4] This situation is somewhat surprising since the integrated use of the reactive sites generated from metal NPs/NCs and a suitable support could be a powerful means for the design of multitask catalysts,^[5] thus providing promising candidates to perform sophisticated tandem reactions for synthesis of complex molecular targets from simple and convenient substrates in a domino fashion.^[6]

Quinolines and their derivatives are an important class of bioactive compounds that are prescribed as antimalarial, antibacterial, antihypertensive, and antiinflammatory drugs.^[7] In addition, quinolines are valuable synthons used for the preparation of nanostructures and polymers that combine enhanced electronic, optoelectronic, or nonlinear optical properties with excellent mechanical properties.^[8] The most frequent routes to prepare functionalized quinolines include

several named reactions, such as Skraup,^[9] Doebner–Von Miller,^[10] Conrad–Limpach,^[11] Friedländer,^[12] and Pfizinger^[13] syntheses based on the reaction of substituted anilines with carbonyl compounds. Despite their utility, these methods often suffer from the requirement of costly aromatic amines and unstable carbonyl compounds, harsh conditions, and the use of large amounts of hazardous acids or bases.^[14] More problematic is that the complicated substituted amines must themselves be synthesized first, mostly by multistep procedures.^[15] The development of new strategies to obtain quinolines in a fast, clean, and efficient way has been the focus of considerable efforts.^[16] In this context, the assembly of the quinolines directly from readily available nitroarenes and aliphatic alcohols through a one-pot tandem reaction is highly attractive.^[17] Unfortunately, this straightforward method has proven to be extremely difficult, and effective catalyst systems were severely limited. To date, only two homogeneous transition-metal catalytic systems^[17a,b] and one UV-irradiated photocatalytic system^[17c] have been reported. From a synthetic and economic point of view, these systems are not practically useful because of the inherent problems of non-reusability, the necessity of special handling of an external light source, or harsh conditions, as well as low yields and limited substrate scope.

Herein, we report for the first time that a new heterogeneous iridium-based multitask catalyst facilitates the rapid direct construction of valuable quinolines from nitroarenes and alcohols under mild conditions through a facile sequential transfer reduction–condensation–dehydrogenation pathway. The combination of sub-nanosized iridium clusters with an oxide support possessing suitable surface acidity, for example, TiO₂, provides an optimal catalyst. Iridium was selected because Ir NPs and complexes are well known to catalyze a wide range of organic transformations including dehydrogenation and transfer hydrogenation.^[18] The present heterogeneous Ir-catalyzed process shows several fundamental improvements: 1) unprecedented catalytic efficiency; 2) unique functional group tolerance; 3) avoidance of expensive ligands or additives; 4) reusability of the catalyst; and 5) high-quality products without residual heavy-metal contamination. To the best of our knowledge, the reaction is considerably greener than any of the known procedures and involves an easy workup.

Initially, the direct transformation of nitrobenzene with *n*-propanol to give 2-ethyl-3-methylquinoline (**3a**) was inves-

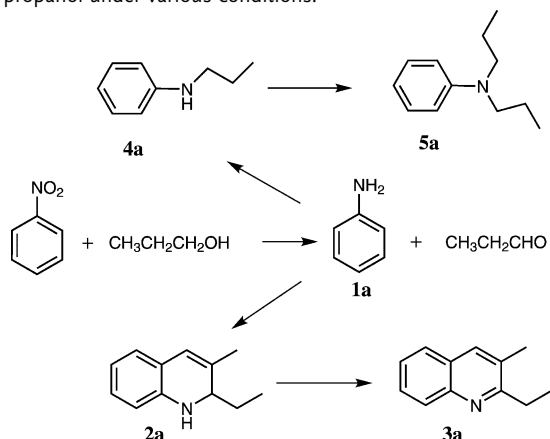
[*] L. He, Y. Gong, Dr. Y. M. Liu, Prof. Dr. Y. Cao, Prof. Dr. H. Y. He, Prof. Dr. K. N. Fan
Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials, Department of Chemistry, Fudan University
Shanghai 200433 (P. R. China)
E-mail: yongcao@fudan.edu.cn

Prof. Dr. J. Q. Wang
Shanghai Institute of Applied Physics, Chinese Academy of Sciences
Shanghai 201204 (P. R. China)

[**] This work was supported by the National Natural Science Foundation of China (20873026 and 21073042), New Century Excellent Talents in the University of China (NCET-09-0305), and the Science and Technology Commission of Shanghai Municipality (08DZ2270500).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201104089>.

Table 1: The synthesis of 2-ethyl-3-methylquinoline from nitrobenzene and propanol under various conditions.^[a]



Entry	Catalyst	t [h]	Conv. [%] ^[f]	1a	2a	Yield [%] ^[f]	3a	4a	5a
1	Ir/TiO ₂ -NPs	8	71	4	1	63	1	1	
2	Ir/CeO ₂	8	55	23	6	7	6	4	
3	Ir/ZnO	8	32	15	7	5	1	2	
4	Ir/SiO ₂	8	9	2	3	1	1	1	
5	Pt/TiO ₂	8	21	7	1	12	tr	tr	
6	Au/TiO ₂	8	41	22	1	11	2	tr	
7	Pd/TiO ₂	8	n.r.	—	—	—	—	—	
8	Ru/TiO ₂	8	n.r.	—	—	—	—	—	
9	Ag/TiO ₂	8	n.r.	—	—	—	—	—	
10	H ₂ IrCl ₆ ·6H ₂ O	8	n.r.	—	—	—	—	—	
11	IrO ₂	8	n.r.	—	—	—	—	—	
12	Ir powder	8	n.r.	—	—	—	—	—	
13	TiO ₂	8	n.r.	—	—	—	—	—	
14	Ir/TiO ₂ -NCs	8	100	tr	3	86	8	2	
15 ^[b]	Ir/TiO ₂ -NCs	8	100	6	2	71	12	3	
16 ^[c]	Ir/TiO ₂ -NCs	1.2	100	tr	1	73	11	13	
17 ^[d]	RuCl ₃	4	100	tr	1	65	5	8	
18 ^[e]	{[Rh(CO) ₂ Cl] ₂ }	4	100	n.m.	n.m.	78	n.m.	n.m.	

[a] Reaction conditions: Nitrobenzene (5 mmol), propanol (20 mL), catalyst (metal: 0.167 mol %) at 120 °C, N₂ atmosphere (5 atm); n.r. = no reaction. tr = trace. n.m. = not measured. [b] Third run. [c] 180 °C.

[d] Reference [17a]: nitrobenzene (40 mmol), propanol (20 mL), catalyst (Ru: 5 mol %) at 180 °C. [e] Reference [17b]: nitrobenzene (10 mmol), propanol (15 mL), catalyst (Rh: 5 mol %), MoCl₅ (Mo: 10 mol %) at 180 °C, Ar atmosphere. [f] Conversions and yields based on nitrobenzene consumption (GC analysis). Note that an appreciable amount of azobenzene was detected in the presence of Au/TiO₂ or Ir/CeO₂.

titigated as a model reaction to identify the potential catalysts.^[19] Summarizing these experiments, we observed that small Ir NPs (average size ca. 1.5 nm) supported on titanium oxide (denoted as Ir/TiO₂-NPs, Ir content: 1 wt %; see the Supporting Information for preparation details) gave an impressive conversion of nitrobenzene to afford **3a** in 63 % yield at 120 °C within 8 h (Table 1, entry 1). Other mineral supports, such as CeO₂, ZnO, and SiO₂ resulted in low yields (Table 1, entries 2–4). Under the same conditions, metal NPs supported on TiO₂, including Pt and Au NPs, gave poor yields (Table 1, entries 5 and 6), whereas Pd, Ru, and Ag NPs were completely inactive (Table 1, entries 7–9). In addition, the use of the catalyst precursor H₂IrCl₆·6H₂O as well as other Ir

compounds, including IrO₂, bulk Ir powder, or parent TiO₂, in place of Ir/TiO₂ NPs did not promote the reaction at all (Table 1, entries 10–13).

Bearing in mind that particle size has been proven to be especially influential for supported metal catalysts,^[20] it is conceived that Ir sub-nanosized clusters (< 1 nm) deposited on TiO₂ could be more effective for the direct tandem synthesis of quinoline. To explore this possibility, an Ir/TiO₂ sample with ultralow loading (0.05 wt %) was prepared. As determined by high-resolution transmission electron microscopy (HRTEM) and the Ir L₃-edge extended X-ray absorption fine structure (EXAFS), most of the Ir species were in the region of sub-nanometers (ca. 0.9 nm, denoted as Ir/TiO₂-NCs, see Figure S2 and Table S3 in the Supporting Information). To our delight, the yield of the desired product **3a** was obtained up to 86 % in the presence of Ir/TiO₂-NCs (Table 1, entry 14). After the reaction, the Ir/TiO₂-NCs could be easily separated by filtration; inductively coupled plasma (ICP) analysis confirmed that no Ir was present in the filtrate, indicating that the observed catalysis is heterogeneous. Furthermore, the recovered Ir/TiO₂-NCs catalyst can be reused, at least three times, while maintaining 100 % conversion and 71 % yield at 120 °C (Table 1, entry 15). There are very few catalysts that are effective under such mild conditions. The previously reported homogeneous ruthenium and rhodium catalytic systems required very harsh conditions (180 °C, 5 mol % Ru or 10 mol % Rh).^[17a,b] We found that, under similar reaction conditions (i.e., 180 °C), the Ir/TiO₂-NCs is about 100 times more active than the previous catalytic systems (Table 1, entries 16–18).

The reaction profiles for the Ir/TiO₂-NCs-catalyzed quinoline formation (see Figure S4 in the Supporting Information) showed that aniline (**1a**) and dihydroquinoline (**2a**) were formed initially.^[21] Furthermore, it was confirmed in separate experiments that the direct conversion of aniline and aldehyde over Ir/TiO₂-NCs gave 67 % yield of **3a**, while the combination of aniline and 2-methyl-2-pentenal, the self-aldol condensation product of propanal, led to **3a** as a major product (59 % yield). These results indicate that the direct synthesis of quinoline would proceed through a series of consecutive steps in a cascade mode (see Scheme S1 in the Supporting Information), in which the initial steps must be the dehydrogenation of alcohols and transfer hydrogenation of nitrobenzene, generating aminoarenes and aldehydes. Then, acid-catalyzed Michael addition of aniline to the self-aldol condensation product might occur, followed by ring closure with dehydration to form dihydroquinoline, which would be finally dehydrogenated to afford the quinoline products.

To clarify the essential role of Ir/TiO₂-NCs for the title reaction, we investigated the catalytic performance for the direct conversion of aniline and aldehyde at 120 °C over different Ir-free supports. As depicted in Table S1, TiO₂ possessing mild surface acidity gave 41 % yield of 2-ethyl-3-methyl-1,2-dihydroquinoline (**2a**) in 8 h (Table S1, entry 1), whereas CeO₂ and ZnO with basic character and SiO₂ with acidic character resulted in low yield of the dihydroquinoline intermediate (Table S1, entries 2–4). These results suggest that the inherent surface nature of TiO₂ is critical in mediating

the condensation–cyclization steps involved in quinoline formation. Moreover, the lack of any nitrobenzene and alcohol transformation over pure TiO_2 strongly confirms that the sub-nanosized Ir clusters were indispensable for promoting the initial transfer reduction of nitrobenzene by using alcohol as an in situ source of hydrogen. Furthermore, examination of a series of Ir/ TiO_2 samples with various Ir loadings (0.05, 1, 5 wt %) demonstrated that iridium clusters with smaller particle size gave higher intrinsic activity for direct quinoline synthesis from nitrobenzene and alcohol (Table S2, entries 1–3), indicating that high dispersion of Ir is beneficial for the key hydrogenation and dehydrogenation steps. Taken together, these results indicate that a delicate balance of cooperation between the sub-nanosized Ir clusters and the acid sites of the TiO_2 surface is essential to facilitate the desired reaction in a domino fashion.

With these findings in hand, we started to extend this direct tandem synthesis of quinoline derivatives to a wider range of alcohols and nitroarenes (Table 2). Other aliphatic alcohols, including ethanol, butanol, pentanol, and hexanol, gave the corresponding 2,3-disubstituted quinolines in remarkably high yields (Table 2, entries 1, 3–5), considering the steps involved. Nitrobenzenes with electron-donating and electron-withdrawing groups in various positions reacted smoothly (Table 2, entries 6–14). In the transformations of methylnitrobenzenes, the lower reaction rate of *o*-methylnitrobenzene relative to the *m*- and *p*-analogues indicates a steric effect that may block ring closure to form the quinoline skeletons (Table 2, entries 6–8). Chloro-substituted nitrobenzenes converted into the corresponding chloro alkyl quinolines without any dehalogenation (Table 2, entries 9 and 10), which was encountered in other catalytic procedures.^[17c] To further demonstrate the general applicability of our procedure, we were interested in the functional group tolerance of the catalytic system. Therefore, we studied especially challenging substrates that might undergo additional reductive transformations. As depicted in Table 2, by employing nitrobenzenes with sensitive substitutes such as ketone, olefin, and carboxylic ester group as the reactants, the corresponding quinolines were obtained in fairly good to excellent yields (Table 2, entries 12–14). To the best of our knowledge, there is no other example of this type of selectivity in quinolines construction from nitroarenes and aliphatic alcohols.

More importantly, the present heterogeneous tandem synthesis of quinolines could be scaled up. For example, the direct conversion of nitrobenzene (50 mmol) and propanol in the presence of Ir/ TiO_2 -NCs (0.0167 mol %) at 180 °C proceeds smoothly to afford 2-ethyl-3-methylquinoline in 70 % yield within 15 h (Table 2, entry 15). In this case, unprecedented catalyst productivity with turnover numbers (TON) of up to 6000 was realized.

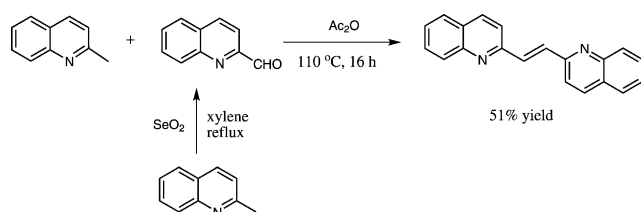
Given the importance of the quinoline nucleus in medicinal chemistry and the excellent performance of Ir-catalyzed quinoline synthesis under mild conditions, we thought that the high quality alkyl quinoline obtained could be utilized for the design of pharmacologically active compounds. One such target with fundamental biological interest is 2-alkenyl bisquinoline, a structure that exhibits significant activity against intracellular amastigotes forms of

Table 2: Synthesis of quinoline derivatives from substituted nitroarenes and aliphatic alcohols.^[a]

$\text{RCH}_2\text{CH}_2\text{OH} + \text{X-C}_6\text{H}_4\text{-NO}_2 \xrightarrow[120^\circ\text{C}]{\text{Ir/TiO}_2\text{-NCs}} \text{Quinoline derivative}$					
Entry	Nitroarene	Alcohol R =	Product	t [h]	Yield [%] ^[b]
1		H		28	78 (74)
2		CH ₃		8	86 (83)
3		C ₂ H ₅		8	92 (89)
4		<i>n</i> -C ₃ H ₇		7	85 (81)
5		<i>n</i> -C ₄ H ₉		7	87 (84)
6		CH ₃		24	71 (66)
7 ^[c]		CH ₃		16	76 (71)
8		CH ₃		10	69 (65)
9 ^[c]		CH ₃		10	60 (54)
10 ^[d]		CH ₃		10	67 (63)
11		CH ₃		18	78 (76)
12		CH ₃		26	68 (62)
13		CH ₃		17	69 (65)
14 ^[d]		CH ₃		28	68 (62)
15 ^[e]		CH ₃		15	70 (68)

[a] Reaction conditions: Nitroarene (5 mmol), alcohol (20 mL), Ir/ TiO_2 -NCs (Ir: 0.167 mol %) at 120 °C under N₂ atmosphere (5 atm). Yields were based on nitroarenes consumption (GC analysis). [b] Values in parentheses refer to yields of isolated product. [c] Less than 3 % 2,3,5-substituted quinolines was detected. [d] 150 °C. [e] Nitroarene (50 mmol), alcohol (50 mL), Ir/ TiO_2 -NCs (Ir: 0.0167 mol %) at 180 °C under N₂ atmosphere (5 atm).

L. amazonensis and *L. infantum* and also against the replication of HIV-1.^[22] To this end, 2-((*E*)-2-(quinolin-2-yl)vinyl)-quinoline was synthesized in 51 % yield (see Scheme 1) by a convergent synthetic approach,^[23] employing 2-methylquinoline and 2-quinolaldehyde as the reactants; the latter is



Scheme 1. Synthesis of 2-alkenyl bisquinoline from 2-methyl quinoline.

accessible from 2-methylquinoline through a simple oxidation process (see details in the Supporting Information).^[24]

In conclusion, we have reported the noteworthy features of the ligand-free Ir/TiO₂-NCs catalyst for the heterogeneously catalyzed tandem synthesis of valuable quinoline compounds from nitroarenes and aliphatic alcohols under mild and additive-free conditions. The ready availability of the substrates and the excellent substrate tolerance observed make this protocol attractive for rapidly generating a library of functionalized quinoline derivatives that are of tremendous importance in medicinal chemistry.

Experimental Section

General procedure for the direct synthesis of quinolines from nitroarenes and aliphatic alcohols: A mixture of nitrobenzene (5 mmol), alcohol (20 mL), and catalyst (metal: 0.167 mol %) was charged into an autoclave (100 mL capacity). The resulting mixture was vigorously stirred (1000 rpm with a magnetic stir bar) at 120 °C under N₂ atmosphere (5 atm) for the given reaction time. The products were confirmed by comparison of their GC retention time and mass, ¹H, and ¹³C NMR spectra. The conversion and product selectivity were determined by a GC-17 A gas chromatograph equipped with a HP-5 column (30 m × 0.25 mm) and a flame ionization detector (FID). For isolation, the combined organic layer was dried over anhydrous Na₂SO₄, concentrated, and purified by silica gel column chromatography.

Received: June 15, 2011

Published online: August 26, 2011

Keywords: alcohols · arenes · cluster compounds · heterogeneous catalysis · iridium

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- [19] By regulating the conditions used in various preparation techniques (see the Supporting Information for experimental details), we were able to control the mean size of different metal nanoparticles on various supports (1 wt %) in the range 1.5–2.5 nm. Typical transmission electron microscopy (TEM) micro-

graphs and corresponding metal particle size distributions for the catalysts are shown in Figure S1.

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