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Heterogeneous Gold-Catalyzed Selective Reductive Transformation of Quinolines with Formic Acid

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Abstract: Single phase rutile titania supported gold nanoparticles (Au/TiO_2-R) are found to be efficient and versatile catalysts for chemo- and regioselective transfer hydrogenation of quinoline derivatives to 1,2,3,4-tetrahydroquinolines (THQs) using formic acid (FA) as a safe and convenient hydrogen source under mild conditions. The activity and chemoselectivity of the Au/TiO_2-R catalyst towards THQs is excellent, with a substrate to catalyst ratio (S/C) of 1000 being feasible. Furthermore, a straightforward and selective route to *N*-formyltetrahydroquinolines (FTHQ) directly from quinoline compounds and FA by one-pot, gold-catalyzed reductive N-formylation protocol is also established.

Keywords: gold; heterogeneous catalyst; nanoparticles; N-formylation; quinolines; transfer hydrogenation

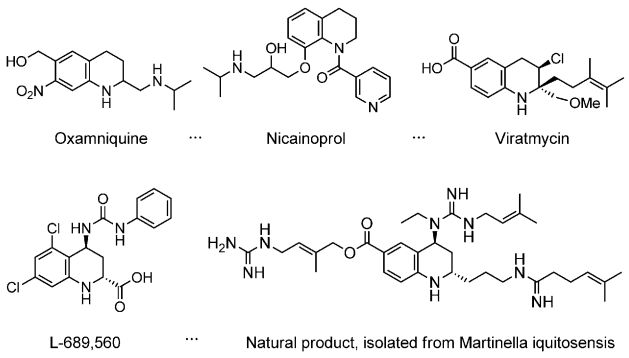


Figure 1. THQ derivatives as prescription or potential drugs.

1,2,3,4-Tetrahydroquinolines (THQs), which structurally exist in numerous natural products and synthetic bioactive compounds, have attracted much attention in the chemical and pharmaceutical industries.[1] For instance, among well-known prescription or potential drugs are the THQ derivatives Oxamniquine used for treatment of Schistosoma mansoni infection,[2] Nicainoprol for cardiac arrhythmis,[3] Viratmycin as a novel antibiotic,[4] L-689,560 as one of the most potent NMDA antagonists[5] and a natural product, isolated from Martinella iquitosensis, as a hradykinin antagonist (Figure 1).[6] Given their immense pharmaceutical utility, the synthesis of THQs has been extensively studied.[7] The most common route to THQs is the hydrogenation of readily accessible quinolines. Such type of reactions are usually carried out using molecular hydrogen,[8] with two major drawbacks:[9,10] high H_2 pressure is typically required and the stoichiometry of H_2 is difficult to control, oftentimes leading to substrate over-reduction. A more attractive alternative is to use catalytic transfer hydrogenation (CTH),[11] which can be efficiently performed without the use of sophisticated instruments (autoclave) or H_2 gas. In this regard, a number of homogeneous as well as heterogeneous catalytic systems in combination with different hydrogen donors have been developed.[7–11] However, despite their potential utility, these methods suffer from one or more drawbacks such as the use of expensive ligands, hazardous or toxic reducing agents, limited substrate scope, and poor chemoselectivity. Therefore, it remains a great challenge to develop a ligand-free, heterogeneous CTH system that can reduce quinolines in a general, efficient, selective, safe and convenient manner.

N-Formyltetrahydroquinolines (FTHQs), an important class of derivatives to THQs, also show a variety of pharmacological properties and minor changes of their structure offer a high degree of diversity that has proven useful for the search of new therapeutic agents.[12] Although FTHQ compounds occur less often in nature and offers less potential structural multiplicity, the broad spectrum of pharmacological activity of these heterocycles led nevertheless to the elaboration of concise and flexible synthetic methods

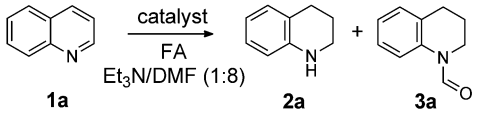
useful in the production of specific structures.[2–6] FTHQs can be directly accessed via N-formylation from THQs, with formic acid (FA) being the most commonly used formylating reagents. FA is one of the major by-products formed during biomass processing and is also easily accessible by methyl formate hydrolysis or CO_2 hydrogenation.[13] As a result of an ongoing demand for new strategies that can allow safe and renewable energy storage, the use of FA as a hydrogen storage material has received much attention over the past decade.[14] As a hydrogen source, it has many advantages with regards to storage and handling, and therefore has been frequently used in CTH reactions.[15] Given the versatile nature of FA, the direct one-pot reductive N-formylation of quinolines using FA is envisioned as an appealing approach to access FTHQs. With regard to green synthesis, this approach is particularly attractive given the use of FA as an inexpensive and sustainable reagent as well as the step economy as compared to traditional multistep procedures. A very recent report describes the use of pyrophoric palladium on activated charcoal (Pd/C) as the catalyst for this particular transformation.[16] However, the inherent limitations of high catalyst loading, high excess of FA and necessity of special handling have restricted the utility of this procedure.

In the course of our continuing efforts in developing green catalysis for sustainable synthesis, we have discovered an efficient approach for mild and clean hydrogenation of a wide range of quinoline compounds to the corresponding THQs using titania supported gold nanoparticles (NPs).[8d] An interesting feature of this heterogeneous Au-catalyzed quinoline hydrogenation reaction is that an unusual reactant-promoted H_2 activation has been identified, which is in stark contrast to what prevails in the traditional platinum-group-metal-based catalytic systems,[17] in which quinolines and their derivatives typically act as poisons. We have also made great efforts in the exploitation of FA activation, wherein we found that zirconia supported gold NPs can promote efficient H_2 generation via selective FA dehydrogenation under ambient conditions.[18] With the aim to develop innovative catalytic processes that enable chemical transformations to be performed under mild and sustainable conditions with high efficiency, we decided to evaluate the catalytic activity of supported gold for the partial reduction of quinolines with FA. Herein, we report that by using a single-phase rutile titania supported gold catalyst, it is possible to realize a versatile transfer reduction of a range of functionalized quinolines to their corresponding THQs utilizing FA as a safe and economically more favored hydrogen source. To the best of our knowledge, this study reports the first direct one-pot conversion of quinoline compounds to FTHQs by reductive N-formylation in the presence of a gold catalyst.

First, we investigated the selective reduction of quinoline (**1a**) in the presence of FA and a range of Au NPs (average diameter of approximately 2-3 nm) deposited on various inorganic oxide materials. We found that such reactions proceeded at a S/C ratio of 100:1 when 10 equivalents of FA in a mixed solvent, Et_3N/DMF in a 1:8 v/v ratio, was used at 100 °C.[19] We initially investigated the previously reported zirconia supported gold catalyst system comprising small Au NPs (approx. 1.8 nm) deposited on acid-tolerant zirconia (Au/ZrO_2), which has been identified as a very effective catalyst for low temperature dehydrogenation of FA to produce CO-free hydrogen. Unfortunately, the reduction hardly occurred and only a very limited amount of THQ (**2a**) was formed (Table 1, entry 1). Attempts to extend the reaction time or varying the reaction temperature failed to promote the reduction of **1a** (Table 1, entries 2-4). Interestingly, when applying a commercial biphasic titania (Evonik P25) supported gold catalyst (Au/TiO_2-P25, average gold particle size ~2.6 nm), which has been widely studied and proven to be highly effective for a variety of organic transformations including chemoselective nitro reduction, selective alcohol oxidation, and nitrile hydration reactions for amide formation,[20] appreciable levels of reduction activity was observed, thus furnishing the desired **2a** in a yield of approximately 37% (Table 1, entry 5). Further evaluation of a series of titania polymorphs supported gold catalysts with identical average Au particle size revealed that an impressive yield of **2a** of about 78% can be attained with a catalyst comprised of gold deposited on single-phase rutile titania (Au/TiO_2-R) (Table 1, entry 6).

Encouraged by these promising results, a more detailed study on the effects of reaction conditions has been carried out with the Au/TiO_2-R catalyst. We focused on the effect of the molar ratio of FA to **1a** under otherwise identical reaction conditions. It turns out that the reaction of **1a** with 15 equiv of FA gave the best results (Table 1, entry 15). Use of 5 equiv of FA led to incomplete conversion of **1a**, and only a limited amount of the desired **2a** could be obtained (entry 14). Upon increasing the FA/**1a** ratio from 5 to 15, the reaction proceeds to completion with a significant increase in the yield of the product (**2a**) (entries 6, 14 and 15). This result suggests that the composition of the reaction medium was critical for the desired reaction pathway. However, lower yields as a result of **3a** formation via further N-formylation of **2a** were observed when 20 equiv of FA were employed (Table 1, entry 16). Notably, further improvements were achieved by performing the reaction at an elevated temperature of 130 °C using 15 equiv of FA,

Table 1. Reduction of quinoline to THQ under CTH conditions.[a]



Entry	Catalyst	FA [equiv]	Time [min]	Temp. [°C]	Conversion [%]	Yield [%][b] 2a	3a
1	Au/ZrO_2	10	60	100	16	16	0
2	Au/ZrO_2	10	120	100	16	16	0
3	Au/ZrO_2	10	60	80	14	6	0
4	Au/ZrO_2	10	60	130	24	24	0
5	Au/TiO_2-P25	10	60	100	37	37	0
6	Au/TiO_2-R	10	30	100	79	78	1
7	Au/TiO_2-A	10	60	100	16	16	0
8	TiO_2-R	10	30	100	0	0	0
9	Au/ZnO	10	180	100	6	0	1
10	Au/Al_2O_3	10	180	100	10	10	0
11	Pd/C	10	180	100	5	0	3
12	Ru/C	10	180	100	7	2	1
13	$Ir/CaCO_3$	10	180	100	13	1	9
14	Au/TiO_2-R	5	30	100	37	37	0
15	Au/TiO_2-R	15	30	100	94	92	2
16	Au/TiO_2-R	20	30	100	98	91	7
17	Au/TiO_2-R	15	10	130	99	96	3
18[c]	Au/TiO_2-R	15	10	130	98	94	4
19[d]	Au/TiO_2-R	15	30	130	95	89	6
20[e]	Au/TiO_2-R	13	60	130	88	80	8

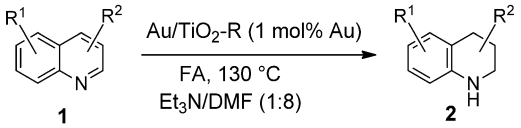
[a] Reaction Conditions: quinoline (0.5 mmol), catalyst (metal: 1 mol%), Et_3N/DMF (1:8 v/v, 3 mL).
[b] Conversion and yield were determined by GC and GC-MS.
[c] Result for the third run.
[d] Au: 0.25 mol%
[e] Au: 0.1 mol%

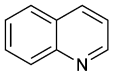
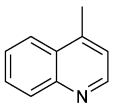
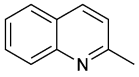
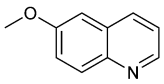
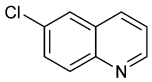
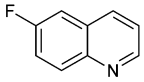
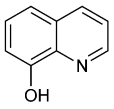
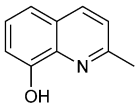
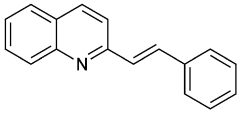
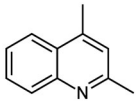
which permit access to **2a** in 96% yield in a very short time of 10 min (Table 1, entry 17).

Upon decreasing the catalyst loading to 0.25 mol%, **2a** was formed in nearly quantitative yield albeit a longer reaction time of ca. 30 min was required (Table 1, entry 19). The transfer reduction was still operative with only 0.1 mol% of the Au/TiO_2-R, and under these conditions remarkable values of the turnover number (TON = 800) and average turnover frequency (TOF = 800 h^{-1}) were calculated (Table 1, entry 20). These values are two orders of magnitude greater than those in the previously reported catalyst systems, such as the nanoporous gold-organosilane combinations (TOF: 1.8 h^{-1}, TON: 43, reaction at 80 °C).[11b,21] At this juncture, it is important to note that gold deposited on single-phase anatase titania (Au/TiO_2-A) can only afford a very moderate yield of **2a** (Table 1, entry 7), in line with the broad literature documenting the effect of polymorphic structure on the activity of titania-based catalysts.[22] The superior activity found for Au/TiO_2-R with respect to Au/TiO_2-P25 and Au/TiO_2-A in this reaction could be due to a higher adsorption capacity of both FA and the quinoline compounds of the Au/TiO_2-R catalyst. The high efficiency of Au/TiO_2-R for the chemoselecive reduction of **1a** using FA relative to other supported gold catalysts was shown clearly (Table 1). Au/Al_2O_3 resulted in poor yields, whereas Au/ZnO did not promote the reduction at all (Table 1, entries 9 and 10). These results show that the combination of Au NPs with suitable polymorphs of titania is essential for achieving a high catalytic activity for the selective reduction of **1a** into **2a** using FA under mild conditions. Moreover, consistent with the case identified for catalytic dehydrogenation of liquid FA under mild conditions,[18] we found that gold is uniquely active for quinoline reduction with FA compared with other noble metals (Table 1, entries 11-13). Among the various catalysts examined here small Au NPs deposited on single-phase rutile titania (Au/TiO_2-R) affords, by far, the best catalytic performance.

To gain more detailed insight into the reaction performed with Au/TiO_2-R, the time-course plot for the above mentioned FA-mediated quinoline reduction was examined at a S/C ratio of 400:1 (Supporting Information Figure S1). It was found that the reaction

Table 2. CTH of quinolines to THQs with FA in the presence of Au/TiO_2-R.[a]

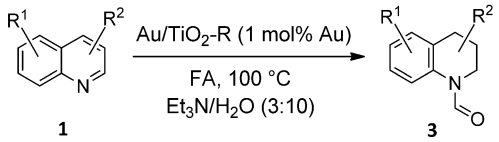


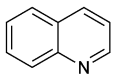
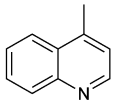
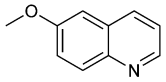
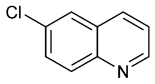
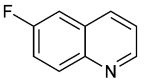
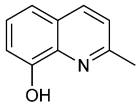
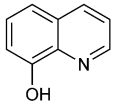
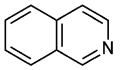
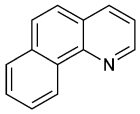
Entry	Substrate	FA [equiv]	Time [min]	Conversion [%]	Yield [%][b]
1		15	10	99	96 (90)
2		20	20	99	94 (89)
3		20	25	99	98 (92)
4		35	40	93	90 (82)
5		20	15	95	90 (84)
6		20	20	90	88 (80)
7		20	20	98	96 (88)
8		30	30	95	94 (85)
9[c]		20	25	99	98 (93)
10		45	50	97	90 (80)

[a] Reaction Conditions: quinoline (0.5 mmol), Au (1 mol%), Et_3N/DMF (1:8 v/v, 3 mL), 130 °C.
[b] Conversion and yield were determined by GC and GC-MS; values in parenthesis are the yields of the isolated products.
[c] The product is 2-phenethyl-1,2,3,4-tetrahydroquinoline.

proceeds smoothly and goes to completion within 30 min. During the whole reaction process, **2a** was the predominant product with only very trace amount of **3a** detected as a by-product. To determine whether Au/TiO_2-R worked as a heterogeneous catalyst, Au/TiO_2-R was removed from the reaction mixture by simple filtration at 50% conversion of **1a**. Continued stirring of the filtrate under similar conditions did not give any products. The absence of Au ions in the filtrate was verified using ICP analysis (detection limit: 0.10 ppm). These results clearly demonstrate that reduction took place only on the Au NPs deposited on TiO_2-R. Furthermore, the Au/TiO_2-R catalyst was recoverable by simple filtration after the transfer reduction without any loss in their activity; images of Au/TiO_2-R after the reuse reveal that the average diameter and size distribution of the gold NPs were similar to those of the fresh Au/TiO_2-R (Supporting Information Figure S2). Also no aggregation of the used gold NPs was apparent. In addition, XPS analysis of Au/TiO_2-R showed virtually no change in the metallic state or dispersion of gold (Supporting Information Figure S3), corroborating the observation that the gold NPs after reuse were the same size after recy-

Table 3. Direct reductive N-formylation of quinolines with FA using Au/TiO2-R.[a]



Entry	Substrate	Time [h]	Conversion [%]	Yield [%][b]
1		5	>99	97 (92)
2[c]		10	>99	95 (89)
3		8	98	92 (84)
4		6	>99	94 (88)
5		5	>99	96 (90)
6		9	95	90 (80)
7[d]		4	>99	86 (78)
8		11	96	95 (90)
9		10	95	93 (85)

[a] Reaction Conditions: quinoline (0.5 mmol), Au (1 mol%), FA (12.5 mmol), Et_3N/H_2O (3:10 v/v, 3 mL), 100 °C.
[b] Conversion and yield were determined by GC and GC-MS; values in parenthesis are the yields of the isolated products.
[c] 130 °C, 6.5 mmol FA was added after 6 h.
[d] 130 °C

cling compared to that in the original sample. These results are consistent with the retention of the catalytic activities of Au/TiO_2-R during recycling experiments.

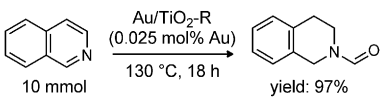
Building upon these results, we started to extend this novel Au-FA-based transfer reduction protocol to a structurally diverse range of quinoline derivatives. As depicted in Table 2, the reaction was remarkably selective for the synthesis of various THQs regardless of the presence of electron donor or acceptor substituents (Table 2, entries 2-11). Quinolines bearing a methyl group at the 2- and 4-position could react smoothly, providing the corresponding THQs in high yields (Table 2, entries 2 and 3). Halogen-substituted quinolines were cleanly reduced to the corresponding chloro or fluoro THQs without any dehalogenation over Au/TiO_2-R (Table 2, entries 5 and 6), which was often encountered on other metal surfaces.[23] Note that the reaction chemistry described herein exemplifies once more the unique nature of gold in catalysis. The selective reduction of 8-hydroxyquinolines afforded the corresponding biologically active THQ (Table 2, entries 7 and 8), which could inhibit leukotriene formation in macrophages.[24] Quinoline derivatives with an alkenyl moiety did not show good chemoselectivity; 2-styryquinoline afforded a major product of 2-phenethyltetrahydroquinoline in 98% yield (Table 2, entry 9). 2,4-dimethylquinoline showed a rel-

atively lower reactivity, giving the corresponding THQ in 90% yield (Table 2, entry 10).

Having established an efficient protocol for the Au-FA-mediated quinoline reduction to prepare THQs, we were then interested in whether this protocol was applicable to the tandem direct transformation of quinolines to FTHQs. With this goal in mind, we have re-explored the effect of solvent on the Au-FA-mediated selective reduction of **1a** at 100 °C. Interestingly, upon switching the mixed organic solvents to a Et_3N/H_2O mixture (1:8 v/v ratio), appreciable formation of FTHQ with a moderate yield well above 60% can be attained even in the presence of just 15 equiv of FA.[19] This result was encouraging and led us to believe that the desired reductive N-formylation pathway may be favored in aqueous-based media. Given the potentially large scale of this conversion, it is important to develop a selective process for the direct transformation of quinolines into FTHQs that can minimize the required amount of FA. We thus decided to investigate the reaction in the cosolvent of Et_3N/H_2O with various volume ratios. To our delight, the use of a 3:10 Et_3N/H_2O mixture together with 25 equiv of FA gave excellent results, with 99% conversion and a high yield well above 97% towards FTHQ. By using this newly established procedure, a variety of quinolines bearing electron-withdrawing and electron-donating subsituents can be converted to their corresponding FTHQs under the aqueous-based conditions as depicted in Table 3.

The utility of this direct reductive N-formylation methodology is further exemplified in the straight-forward and efficient one-pot synthesis of a diversity of formyl-substituted aromatic N-heterocycles by using isoquinoline and 7,8-benzoquinoline and again only 25 equiv of FA as starting materials (Table 3, entries 8 and 9).[25] To further showcase the effectiveness of this direct reductive N-formylation system, we carried out the direct reductive N-formylation of isoquinoline on a one-gram scale (Scheme 1). Direct one-pot N-formylation of isoquinoline (1.29 g) in the 3:10 Et_3N/H_2O mixture with an even lower catalyst loading of 0.025 mol% (100 mg Au/TiO_2-R) in air provided the valuable *N*-formyltetrahydroisoquinoline in 97% isolated yield. This appears to us to be the most efficient way for accessing this type of compound, regarding cost, effectiveness, practicability and scalability.

In conclusion, we have developed a simple, efficient and robust protocol for the chemoselective transfer reduction of quinolines. By using single phase rutile titania supported gold nanoparticles as catalyst and renewable FA as hydrogen source, various quinoline derivatives were reduced to give the THQs in high yields with excellent regioselectivity. More interestingly, this gold-FA-based CTH system could also accomplish the direct conversion of quinoline compounds bearing different functional groups to the corresponding FTHQs chemoselectively, providing a valuable alternative to currently used methods for heterocycle transformation.



Scheme 1. Direct reductive N-formylation of isoquinoline on a one-gram scale.

Experimental Section

General Procedure for THQ Synthesis via Gold-Catalyzed Selective Reduction of Quinolines

Supported gold catalyst (0.005 mmol Au) was placed in a 10 mL round-bottom flask, followed by the addition of quinoline (0.5 mmol), formic acid (the given amount), and Et_3N/DMF (1:8 v/v, 3 mL). The reaction mixture was then vigorously stirred (800 rpm with a magnetic stir bar) at the designated temperature for the given reaction time. After completion of the reaction, the reaction mixture was filtered and the catalyst was washed thoroughly with ethanol. Then the filtrate was washed with water and extracted by ethyl acetate. The mixture was concentrated and dried under reduced pressure using a rotatory evaporator. The crude product was purified by column chromatography [silica gel (200–300 mesh); petroleum ether (60~90 °C)/ethyl acetate mixture] to afford the product. All the products were identified by GC-MS and the spectra obtained were compared with the standard spectra. The conversion and yields were determined by Agilent 7820 A gas chromatograph equipped with a HP-WAX column (30 m × 0.32 mm) and a flame ionization detector (FID).

General Procedure for FTHQ Synthesis via Gold-Catalyzed Reductive N-Formylation of Quinolines

Supported gold catalyst (0.005 mmol Au) was placed in a 10 mL round-bottom flask, followed by the addition of quinoline (0.5 mmol), formic acid (12.5 mmol), and Et_3N/H_2O (3:10 v/v, 3 mL). The reaction mixture was then vigorously stirred (800 rpm with a magnetic stir bar) at the designated temperature for the given reaction time. After completion of the reaction, the reaction mixture was filtered and the catalyst was washed thoroughly with ethanol. The filtrate was washed with water and extracted by ethyl acetate. Then the mixture was concentrated and dried under reduced pressure using a rotatory evaporator. The crude product was purified by column chromatography [silica gel (200–300 mesh); petroleum ether (60~90 °C)/ethyl acetate mixture] to afford the product. All the products were identified by GC-MS and the spectra obtained were compared with the standard spectra. The conversion and yields were determined by Agilent 7820 A GC equipped with a HP-WAX column (30 m × 0.32 mm) and a FID.

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