

Multifunctional catalysis of a ruthenium-grafted hydrotalcite: one-pot synthesis of quinolines from 2-aminobenzyl alcohol and various carbonyl compounds via aerobic oxidation and aldol reaction

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Received 21 April 2004; revised 3 June 2004; accepted 4 June 2004
Available online 24 June 2004

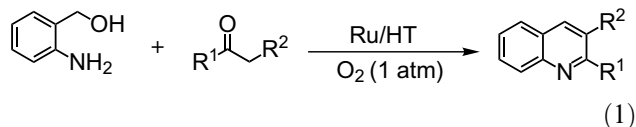
Abstract—The Ru-grafted hydrotalcite was found to be an excellent multifunctional catalyst for one-pot synthesis of quinolines from 2-aminobenzyl alcohol and various carbonyl compounds. These quinolines were obtained through aerobic oxidation by the Ru species, followed by aldol reaction on base sites of the hydrotalcite.

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One-pot syntheses that involve economically and environmentally friendly chemical processes, have received attention as a next strategy for ‘green’ organic syntheses.^{1,2} Solid catalysts that accommodate various active sites on their surface show promise for promoting multiple reactions in a single pot.³ Hydrotalcites (HTs) are useful solid catalysts for nano-scale design of active sites because of their unique properties such as alternating cationic and anionic layers, surface tunable basicity, and adsorption capacity.^{4–6} Recently, we succeeded in preparing a Ru-grafted hydrotalcite (Ru/HT), a multifunctional heterogeneous catalyst, for direct α -alkylation of nitriles via several sequential reactions through cooperative action of Ru species and base sites.⁷

The quinoline nucleus plays an important role as an intermediate in the design of pharmacologically active compounds,⁸ and many synthetic routes of quinolines have been developed. Shim and co-workers proposed the direct formation of quinolines from 2-aminobenzyl alcohol and ketones via hydrogen transfer reaction and cyclization mediated by a homogeneous Ru complex

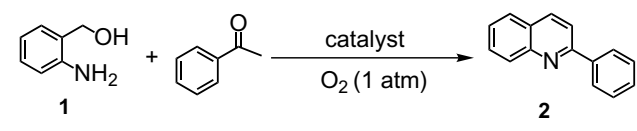
catalyst system with a stoichiometric amount of KOH.⁹ This one-pot method is superior to traditional Friedlander quinoline synthesis¹⁰ because 2-aminobenzyl alcohol is less expensive and more stable than is 2-aminobenzaldehyde. Herein, we report a more environmentally benign one-pot quinoline synthesis from 2-aminobenzyl alcohol and various carbonyl compounds using the heterogeneous Ru/HT catalyst without homogeneous bases (Eq. 1). The present catalytic system described here has significant advantages over catalysts previously reported,⁹ including: (i) high catalytic activity and wide applicability to various carbonyl compounds; (ii) no need for homogeneous bases; and (iii) the use of molecular oxygen as a green oxidant. *This is the first reported one-pot quinoline synthesis using heterogeneous catalysts.*



Preparation of the Ru/HT in the presence of triethylamine (Ru/HT-N) is as follows. A 3.33×10^{-3} M aqueous solution of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (60 mL) was slowly added to the mixture of a hydrotalcite (HT),¹¹ $\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3$ (2.0 g), and triethylamine (10 mmol) in water (140 mL) with vigorous stirring. Then, the

Keywords: Quinoline synthesis; 2-Aminobenzyl alcohol; Heterogeneous catalyst; Hydrotalcite; Ruthenium; Molecular oxygen.

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Table 1. One-pot quinoline synthesis using various catalysts^a


Entry	Catalyst	Conv'n of 1 (%) ^b	Yield of 2 (%) ^b
1	Ru/HT-N	>99	87
2	Ru/HT	>99	61
3	Ru/Al ₂ O ₃	>99 ^c	3
4	Ru/MgO	37	Trace
5	Ru/Al(OH) ₃	33	Trace
6	Ru/Mg(OH) ₂	54	Trace
7	HT	Trace	Trace

^a **1** (1.0 mmol), acetophenone (1.2 mmol), catalyst (0.3 g, Ru: 3.0 mol%), toluene (5 mL), 100 °C, 20 h, under O₂ atmosphere.

^b Determined by GC.

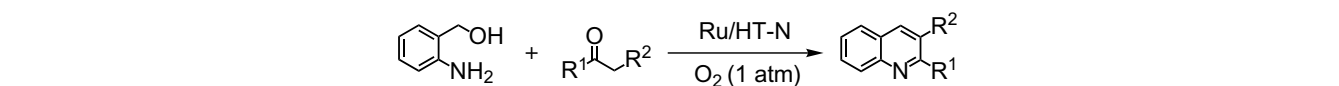
^c Oligomeric products were formed from **1**.

heterogeneous mixture was stirred at 25 °C for 1 h. The solid product was separated by centrifugation, washed thoroughly with deionized water, and dried in vacuo at room temperature, affording the Ru/HT-N as a gray

powder (Ru content: 1.0 wt %). The absence of nitrogen in the Ru/HT-N was confirmed by XPS analysis.

Reaction of 2-aminobenzyl alcohol (**1**) with acetophenone using various kinds of Ru supported catalysts was carried out in the presence of molecular oxygen as shown in Table 1.¹² Interestingly, the Ru/HT-N exhibited the highest catalytic activity to give 2-phenylquinoline in 87% yield (entry 1).¹³ The reactions hardly occurred using the parent HT (entry 7). Other heterogeneous Ru catalysts, such as Ru/Al₂O₃, Ru/MgO, Ru/Mg(OH)₂, and Ru/Al(OH)₃, were inactive for this quinoline synthesis (entries 3–6). Compared with the conventional synthesis method using hydrogen transfer to ketones from **1**,⁹ only 1.2 equiv of ketones were required in this catalyst system.

Quinoline syntheses using various ketones in the presence of the Ru/HT-N catalyst are summarized in Table 2. A wide variety of ketones reacted smoothly with **1**, to give the corresponding quinolines in high yields. The electronic variable substituents on the aromatic ring of acetophenone did not strongly affect the yield of quinolines except for 2'-methylacetophenone (entries 1–9).

Table 2. Quinoline synthesis from various ketones^a


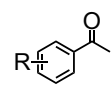
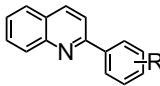
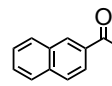
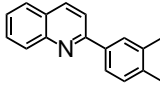
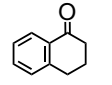
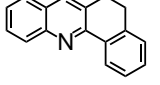
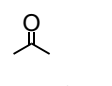
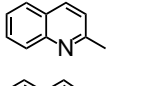
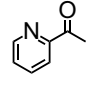
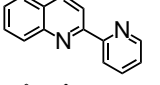
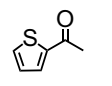
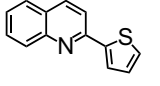
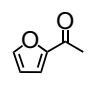
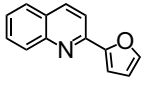
Entry	Ketone	Product	Yield of quinoline ^b (%)
1			84 ^c
2	R = 4-Cl	R = 4-Cl	83 ^c
3	R = 4-F	R = 4-F	90 ^c
4	R = 3-CF ₃	R = 3-CF ₃	78 ^c
5	R = 2-Me	R = 2-Me	35
6	R = 3-Me	R = 3-Me	94 ^c
7	R = 4-Me	R = 4-Me	83 ^c
8	R = 4-OMe	R = 4-OMe	79 ^c
9	R = 4-NO ₂	R = 4-NO ₂	83
10 ^d			89 ^c
11 ^d			74 ^c
12 ^c			74 ^c
13 ^d			88
14 ^d			77
15 ^d			80

Table 2 (continued)

Entry	Ketone	Product	Yield of quinoline ^b (%)
16 ^f			82 ^c
17 ^f			76 ^c
18 ^f			84

^a 2-Aminobenzylalcohol (1 mmol), ketone (1.2 mmol), Ru/HT-N (0.3 g, Ru: 3.0 mol%), toluene (5 mL), 20 h, 100 °C, O₂ (1 atm).

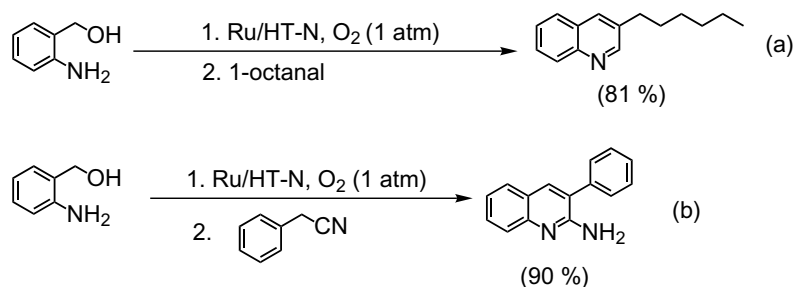
^b Yield was determined by HPLC and GC using an internal standard based on 2-aminobenzyl alcohol.

^c Isolated yield.

^d 150 °C, in a stainless autoclave.

^e 5 mmol of acetone was used in autoclave.

^f HT (0.15 g) was used, 40 h.



Scheme 1. Reagents and conditions: (a) (1) **1** (1 mmol), Ru/HT-N (0.3 g; Ru: 3.0 mol%), toluene (5 mL), 100 °C, 10 h, O₂. (2) 1-Octanal (2 mmol) was slowly added in flask during 12 h at 100 °C; (b) (1) **1** (1 mmol), Ru/HT-N (0.3 g; Ru: 3.0 mol%), toluene (5 mL), 100 °C, 7 h, O₂. (2) Phenylacetonitrile (1.5 mmol), 160 °C, 7 h.

Reactions using 2-acetonaphthone and α -tetralone also yielded 2-naphthylquinoline and 5,6-dihydrobenzo[*c*]acridine, respectively, in high yields (entries 10 and 11). This catalyst system was applicable to the heteroaromatic compounds 2-acetylthiophene, 2-acetylpyridine, and 2-acetylfuran (entries 13–15). A large-scale reaction of **1** with acetophenone afforded the quinoline in 89% isolated yield.¹⁴ It should be noted that the Ru/HT-N catalyst could be reused with retention of a high product yield; a recycling experiment resulted in 81% yield of 2-phenylquinoline.¹⁵ The mechanism of a one-pot quinoline synthesis using the Ru/HT is proposed as follows: the surface Ru species oxidizes 2-aminobenzyl alcohol to 2-aminobenzaldehyde under an O₂ atmosphere,¹⁶ followed by aldol reaction with ketones catalyzed by the base sites of the HT to yield the quinolines.^{7,17}

The applicability of the Ru/HT-catalyzed one-pot synthesis is highlighted by the reaction of α,β -unsaturated ketones with carbon–carbon double bonds that are easily reduced by metal–hydride species.¹⁸ The reactions of benzalacetone derivatives with **1** afforded styryl quinolines, precursors of naturally occurring tetrahydroquinoline alkaloids and inhibitors of viral proliferation,¹⁹ in good yields (Table 2, entries 16–18). Reduction of C–C double bonds did not occur because of the smooth oxidation of the Ru–H species by molecular oxygen. Furthermore, 1-octanal and phenylacetonitrile were also reacted as donors to afford 3-

amylquinoline and 2-amino-3-phenylquinoline in 81% and 90% yields, respectively (Scheme 1). To the best of our knowledge, this is the first example of a one-pot quinoline synthesis from 2-aminobenzyl alcohol with unsaturated ketones, aldehydes, and nitrile compounds.

In summary, the Ru/HT-N acted as an efficient heterogeneous bifunctional catalyst for the one-pot synthesis of substituted quinolines from 2-aminobenzyl alcohols and various carbonyl compounds under atmospheric oxygen.

Acknowledgements

This work is financially supported by the center of excellence (21COE) program ‘Creation of Integrated EcoChemistry’ of Osaka University. We are also grateful to the Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, for scientific support with the gas–hydrate analyzing system (GHAS) and lend-lease laboratory system.

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 - We think that the role of triethylamine is neutralization of HCl generated by the chemical absorption of the Ru species onto the HT surface.
 - A large-scale reaction of 2-aminobenzyl alcohols with acetophenone is as follows. Into Pyrex glass reactor were placed the Ru/HT-N (3.0 g, Ru: 0.3 mmol), toluene (50 mL), 2-aminobenzyl alcohol (1.23 g, 10.0 mmol), and acetophenone (1.44 g, 12.0 mmol). Then, the reaction mixture was vigorously stirred at 100 °C under an O₂ atmosphere. After 20 h, the catalyst was separated by filtration. The filtrate was evaporated, and the crude product was purified by column chromatography (silica gel, ethyl acetate–hexane (1:9) mixture), which afforded the desired product, 2-phenylquinoline (1.82 g, 89% yield).
 - Recycling experiment of the Ru/HT-N is as follows. The reaction of 2-aminobenzyl alcohol (1.0 mmol) and acetophenone (1.2 mmol) in toluene (8 mL) with Ru/HT-N (0.30 g, Ru: 0.03 mmol) and MS4A (0.3 g) was carried out under reflux. After 20 h, the Ru/HT-N was removed by filtration and GC analysis of the filtrate showed an 84% yield of 2-phenylquinoline. The recovered Ru/HT-N was washed with toluene, acetone, and water successively, and then dried in vacuo before reuse. The recycling reaction using the spent Ru/HT-N catalyst afforded the quinoline in 81% GC yield under same reaction conditions.
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