A Ruthenium-Grafted Hydrotalcite as a Multifunctional Catalyst for Direct α-Alkylation of Nitriles with Primary Alcohols

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Controlling the precise architectures of catalytically active species on solid surfaces is one of the most important challenges in the creation of nanostructured heterogeneous catalysts, which has inherent advantages of being operationally simple as well as enabling unprecedented reactions based on multifunctional catalysis by several active sites.[1] Among inorganic crystals, hydrotalcites (HT) have attracted considerable interest because of alternating cationic and anionic layers, surface tunable basicity, and adsorption capacity.[2,3] These unique properties of hydrotalcites will offer an attractive route for the nanoscale design of heterogeneous catalysts aimed at environmentally friendly organic synthesis.[4]

α-Alkylated nitriles are important building blocks in the construction of amides, carboxylic acids, ketones, and biologically active compounds and are traditionally synthesized with alkyl halides using stoichiometric amounts of inorganic bases.[5] Alternatively, catalytic α-alkylation of nitriles with alcohols is particularly attractive from both an economical and an environmental point of view. Some homogeneous transition metal complexes have been developed to accomplish this transformation; however, all such catalysts suffer from either low activity or low stability and also require inorganic bases as additives.[6] In this contribution, we designed a novel Ru-grafted hydrotalcite (Ru/HT) possessing both active Ru^{4+} species and surface base sites as a multifunctional catalyst for this α-alkylation [eq 1]. The catalytic system described here is one powerful candidate for a promising synthetic protocol of alkylated nitriles because of the following advantages: (i) high catalytic activity and selectivity, (ii) homogeneous bases are unnecessary, (iii) there are no byproducts other than water, and (iv) applicability toward a one-pot synthesis. To the best of our knowledge, this is the first report for the α-alkylation of nitriles achieved by a heterogeneous catalyst.

$$R^1 \diagup CN + R^2 \diagup OH \xrightarrow{\text{Ru/HT}} \underset{R^1}{\overset{R^2}{\diagup}} CN + H_2O \quad (1)$$

Treatment of the HT, $Mg_6Al_2(OH)_{16}CO_3$, with an aqueous solution of $RuCl_3 \cdot nH_2O$ at room temperature afforded the Ru/HT as a gray powder. The absence of chlorine was confirmed by XPS and EDAX analyses. XRD peak positions of the Ru/HT were identical to those of the parent hydrotalcite. The Ru K-edge XANES spectrum of the Ru/HT was similar to that of $Ru^{IV}O_2$ but differed from that of $Ru^{III}(acac)_3$. Additionally, the absence of Ru(III) species in the Ru/HT was evidenced by EPR silence. These facts reveal that the Ru species is in the +4 oxidation state.[7] In Fourier transform (FT) of k^3-weighted Ru K-edge EXAFS (Figure 1a), the lack of peaks at around 3.5 Å showed that there were no Ru–Ru bonds on the Ru/HT. The inverse FT of the main peaks was well fitted by the use of six Ru–O and a single Ru–Mg shell parameter.[8] Conclusively, a monomeric Ru(IV) species having one hydroxyl
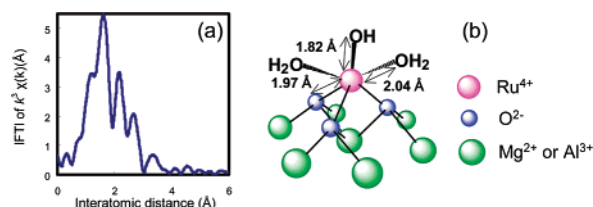

Figure 1. (a) Fourier transform (FT) of k^3-weighted Ru K-edge EXAFS of Ru/HT. (b) A proposed surface structure around Ru^{4+} of Ru/HT.

Table 1. Reaction of Phenylacetonitrile (**1a**) and Ethanol (**2a**) by Various Catalysts[a]

entry	catalyst	yield of **3a** (%)[b]	yield of **4a** (%)[b]
1	Ru/HT	98	trace
2[c]	Ru/HT	trace	10
3	Ru/Al₂O₃	14	trace
4	Ru/MgO	2	trace
5	Ru/Al(OH)₃	5	16
6	Ru/Mg(OH)₂	2	8
7[d]	HT	N.R.[e]	N.R.
8[f]	RuCl₃·nH₂O	N.R.	N.R.

[a] **1a** (1 mmol), **2a** (2 mL), Ru catalyst (0.15 g, Ru: 0.0075 mmol), 20 h, 180 °C, Ar. [b] Based on **1a**. [c] Under O₂. [d] 0.15 g of HT was used. [e] No reaction. [f] 0.0075 mmol of Ru was used.

and two water ligands is grafted onto a triad of oxygen atom on the hydrotalcite surface (Figure 1b).[8] The present preparation, which is much simpler than previous synthetic methods of the solid-supported transition metal catalysts,[9] can allow a strong protocol to create various metal species as catalytically active centers using the surface grafting ability of the HT.

α-Ethylated phenylacetonitrile (**3a**) was obtained by the reaction of phenylacetonitrile (**1a**) with ethanol (**2a**) in the presence of various Ru catalysts under an Ar atmosphere, as shown in Table 1. The Ru/HT catalyst exhibited the highest activity to give 2-phenylbutyronitrile (**3a**) in 98% yield (entry 1). The α-alkylation hardly occurred at all in the presence of only parent HT or $RuCl_3 \cdot nH_2O$ (entries 7 and 8). Other heterogeneous Ru catalysts, such as Ru/Al₂O₃, Ru/MgO, Ru/Mg(OH)₂, and Ru/Al(OH)₃, were found to be less active (entries 3−6). Notably, for the Ru/HT, (Z)-2-phenylcrotononitrile (**4a**) was obtained as the major product under an O₂ atm (entry 2).

The scope of the Ru/HT-catalyzed α-alkylation of various nitriles with alcohols is summarized in Table 2. A wide variety of arylacetonitriles efficiently reacted with **2a**, affording the α-ethylated nitriles in excellent yields without the formation of dialkylated products (entries 1−6). Electronic variation of p-substituted phenylacetonitrile did not strongly affect the reaction rates (entries

Table 2. α-Alkylation of Nitriles with Alcohols Using Ru/HT[a]

$$R^1\diagdown CN + R^2\diagdown OH \xrightarrow{Ru/HT} R^1\diagdown\overset{R^2}{\underset{CN}{\diagup}}$$

| entry	donor		alcohol		product	yield (%)[b]
1	R[1] = Ph	**1a**	R[2] = Me	**2a**	**3a**	98 (94)
2	R[1] = 4-Cl−Ph	**1b**	**2a**		**3b**	83
3	R[1] = 4-Me−Ph	**1c**	**2a**		**3c**	99
4[c]	R[1] = 4-MeO−Ph	**1d**	**2a**		**3d**	92
5[c]	R[1] = 1-naphthyl	**1e**	**2a**		**3e**	89
6[c]	R[1] = 2-thiophenyl	**1f**	**2a**		**3f**	86
7	**1a**		R[2] = H	**2b**	**3g**	65
8	**1a**		R[2] = n-Pr	**2c**	**3h**	94 (86)
9[c]	**1a**		R[2] = i-Pr	**2d**	**3i**	85
10[d,e]	**1a**		R[2] = Ph	**2e**	**3j**	91 (77)
11[d,f]	PhC(O)CH₃	**1g**	**2e**		PhC(O)CH₂Bn	85
12[c,d,g]	i-PrC(O)CH₃	**1h**	**2c**		i-PrC(O)CH₂n-Bu	68

[a] Donor (1 mmol), alcohol (2 mL), Ru/HT (0.15 g, Ru: 0.0075 mmol), 180 °C, 20 h, Ar. [b] Based on donor. Values in parentheses are isolated yield. [c] Ru/HT (0.3 g, Ru: 0.015 mmol). [d] 2 mL of toluene was used. [e] **2e** (1.5 mmol). [f] **2e** (1.0 mmol). [g] **2c** (2.0 mmol).

Scheme 1
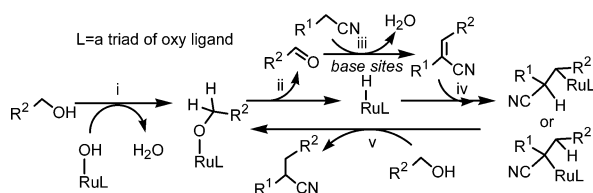
2−4). The α-ethylation of a sterically hindered 1-naphthylaceto-nitrile (**1e**) proceeded successfully to form 2-(1-naphthyl)-butyro-nitrile in high yield (**3e**). The Ru/HT catalyst system was applicable to a heteroarylacetonitrile including a sulfur atom as a donor (**1f**). A diverse set of primary alcohols was usable for this α-alkylation reaction (entries 1, 7−10); interestingly, the reaction of **1a** with n-butanol (**2c**) gave 2-phenylhexanonitrile (**3h**), a precursor of the systemic fungicide Systhane,[5c] in 94% yield. The Ru/HT catalyst could also promote the α-alkylation of carbonyl compounds as a donor (entries 11 and 12). For example, acetophenone (**1g**) reacted with **2e** to produce 1,3-diphenyl-1-propanone (**3k**) in 85% yield. This is the first report for the α-alkylation of ketones with alcohols achieved by a heterogeneous catalyst.[10] A 20 mmol scale reaction of **1a** with **2a** afforded **3a** in 82% yield with a high TOF of 14 h⁻¹ and a high TON of 412, which are considerably higher than those of a previously reported homogeneous Ru catalyst combined with the stoichiometric amount of Na₂CO₃ (TOF, 0.77 h⁻¹; TON, 18).[6]

The hydrogen transfer from benzyl alcohol to (Z)-2-phenylcin-namonitrile in the presence of the Ru/HT yielded 2,3-diphenylpro-pionitrile along with benzaldehyde.[8,11] In a separate experiment, the parent HT promoted aldol condensation of **1a** with benzaldehyde to afford (Z)-2-phenylcinnamonitrile.[8] From the above results, it is reasonable that the present α-alkylation consists of the following three consecutive reactions (Scheme 1): oxidative dehydrogenation of alcohols to aldehydes (i, ii), base-catalyzed aldol condensation of nitriles with aldehydes (iii), and hydrogenation of α,β-unsaturated nitriles with a Ru−H species (iv, v).[12] Upon treatment of the Ru/HT with benzyl alcohol, the IR spectrum showed a signal at 2120 cm⁻¹ assignable to ν(Ru−H).[8,13] Vide supra, the reaction of the Ru−H species with dioxygen might lead to the exclusive formation of the α,β-unsaturated nitrile (Table 1, entry 2).[14]

The applicability of the present Ru/HT catalyst is highlighted by a one-pot synthesis of α,α-dialkylated phenylacetonitriles (Scheme 2). For example, after completion of the alkylation of **1a** with **2a**, acrylonitrile (**5a**) was added and allowed to further react at 150 °C for 1 h. The base-catalyzed Michael reaction occurred to

Scheme 2
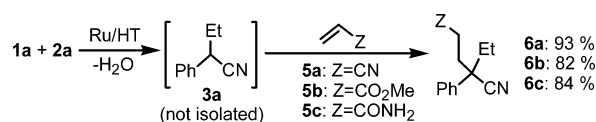
afford 2-ethyl-2-phenylglutarodinitrile (**6a**), a highly useful inter-mediate of sedative Glutethimide,[5b,e] in 93% yield. The conventional method for the synthesis of **6a** from **1a** using iodoethane, NaNH₂, and Triton B gave less than 39% yield.[5b] *For this single pot synthesis, the Ru species and base sites on the Ru/HT surface participate in four sequential reactions: oxidative dehydrogenation, aldol condensation, hydrogenation, and Michael reaction to finally produce α,α-dialkylated phenylacetonitriles.*

In conclusion, the Ru/HT efficiently catalyzed the α-alkylation of a variety of nitriles with alcohols and was further extended for the synthesis of α,α-dialkylated phenylacetonitrile through the co-operative catalysis between the grafted-Ru species and the surface base sites. Nanostructured heterogeneous catalysts, which possess a multifunctional surface, will contribute pivotally in the development of economically and environmentally friendly chemical processes.

Supporting Information Available: Experimental procedure and curve fitting analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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