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One-pot synthesis of α-alkylated nitriles with carbonyl compounds through consecutive aldol reaction/hydrogenation using a hydrotalcite-supported palladium nanoparticle as a multifunctional heterogeneous catalyst

Ken Motokura, Noriaki Fujita, Kohsuke Mori, Tomoo Mizugaki, Kohki Ebitani and Kiyotomi Kaneda*

Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan

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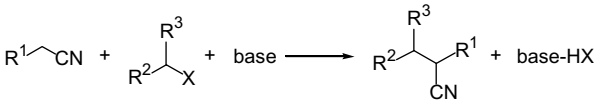
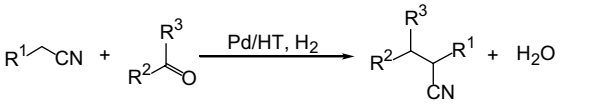
Abstract—α-Alkylation of various nitriles with carbonyl compounds successfully proceeded using a hydrotalcite-supported palladium nanoparticle as a multifunctional catalyst. The alkylated nitriles were formed through aldol reaction at base sites on the hydrotalcite surface followed by hydrogenation by molecular hydrogen on the palladium nanoparticle.

Multifunctional catalysts provide a green and efficient method for the one-pot synthesis of valuable organic compounds in both laboratory and industrial chemistry.[1,2] Of the various types of multifunctional catalyst, solid catalysts with different types of active sites on the surface have attracted considerable interest; their advantages include a simple work-up procedure, the ability to recycle the catalyst, and the easy creation of catalytically active centers on solid surface.[3] Hydrotalcites (HTs), having cation and anion exchange abilities, strong surface basicity, and adsorption ability, are excellent inorganic materials for the evolution of high-performance heterogeneous catalysts.[4–6] We have recently reported the potential use of the HTs as multifunctional catalysts, and reported a ruthenium-grafted hydrotalcite catalyst (Ru/HT) for the one-pot synthesis of α-alkylated nitriles[3c] and quinoline derivatives.[3d]



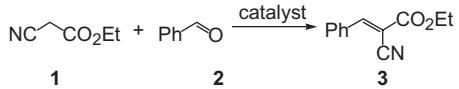
(1)



(2)

From the standpoint of environmental friendliness, the catalytic synthesis of α-alkylated nitriles, which are

Table 1. Aldol reaction of **1** with **2** using various solid base catalysts[a]



1 **2** **3**

Entry	Catalyst	Yield of **3** (%)[b]
1	Pd/HT	99
2	HT	99
3	Al_2O_3	52
4	MgO	3
5	$Al(OH)_3$	2
6	$Mg(OH)_2$	2

[a] **1** (1.0 mmol), **2** (1.0 mmol), catalyst (0.025 g), toluene (3 mL), 80 °C, 1 h.
[b] Determined by GC.

Keywords: α-Alkylation of nitrile; Aldol reaction; Hydrogenation; One-pot synthesis; Palladium; Hydrotalcite; Heterogeneous catalyst.
* Corresponding author. Tel./fax: +81 6 6850 6260; e-mail: kaneda@cheng.es.osaka-u.ac.jp

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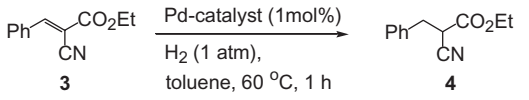
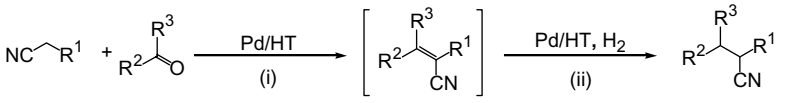


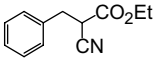
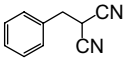
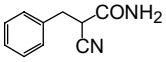
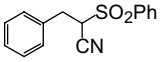
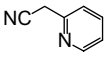
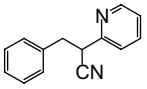
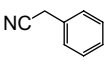
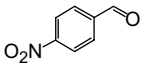
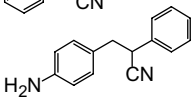
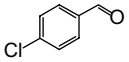
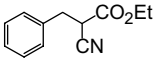
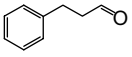
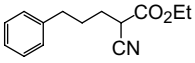
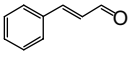
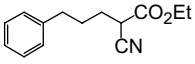
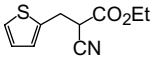
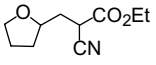
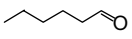
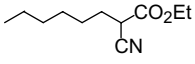
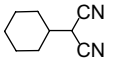
	yield of **4** (%)
Pd/HT	98
Pd/Carbon (0.5 wt%)	94
Pd/Carbon (5.0 wt%)	49

Scheme 1.

important building blocks of various biologically active compounds[7] is attractive: traditional synthetic routes require the use of alkyl halides and strong homogeneous bases in stoichiometric quantities (Eq. 1). We have already demonstrated the effectiveness of the Ru/HT catalyst for direct α-alkylation of nitriles with primary alcohols[3c,8] however, this catalyst system needs a high reaction temperature and is only effective using arylacetonitriles as substrates.[9] In this paper, we report a hydrotalcite-supported palladium nanoparticle catalyst (Pd/HT) for the one-pot α-alkylation of diverse sets of

Table 2. α-Alkylation of various nitriles with carbonyl compounds using the Pd/HT[a]



Entry	Nitrile	Acceptor	Time of (ii) (h)	Product	Yields (%)[b]
1	NC$\frown$$CO_2Et$		1		98
	1	**2**			
2	NC$\frown$CN	**2**	5		82
3[c,d]	NC$\frown$$CONH_2$	**2**	4		95[e]
4	NC$\frown$$SO_2Ph$	**2**	1		99
5		**2**	2.5		99
6[f]			23		84
7[c]	**1**		4		87
8	**1**		1		99
9	**1**		2		98
10	**1**		24		19
11	**1**		3		82
12[c,g]	**1**	HCHO	1		91
13	**1**		1		85(81)
14	NC$\frown$CN		6.5		97(92)

[a] (i): Nitrile (1 mmol), carbonyl compounds (1 mmol), Pd/HT (0.1 g; Pd: 0.01 mmol), toluene (3 mL), 2 h, 80 °C, Ar. (ii): 60 °C, H_2 (1 atm).
[b] Determined by GC using an internal standard. Values in parentheses are isolated yield.
[c] DMF (3 mL) was used as solvent.
[d] (i): 18 h.
[e] Determined by ^{1}H NMR analysis.
[f] (i): 120 °C.
[g] 30% aqueous HCHO was used, (i): 3 h.

nitriles with carbonyl compounds via aldol condensation and hydrogenation (Eq. 2).[10,11]

The Pd/HT was prepared as follows: the HT, $Mg_6Al_2(OH)_{16}CO_3$,[12] (1.0 g) was added to 100 mL of an aqueous $PdCl_2$ (0.1 mmol) solution containing KCl (0.1 g). The heterogeneous mixture was stirred at 25 °C for 1 h under air to afford a pale yellow powder, then successively reduced in the presence of 1 atm H_2 at 100 °C for 8 h. The solid product was isolated by centrifugation, washed thoroughly with deionized water and dried at 110 °C for 12 h, affording the Pd/HT as a black powder (Pd content: 1.0 wt %). The prepared Pd/HT was characterized by X-ray diffraction (XRD), energy-dispersive X-ray spectroscopy (EDX), and transmission electron microscopy (TEM). XRD peak positions of the Pd/HT were identical to those of the parent HT. The absence of chlorine and potassium was confirmed by EDX analysis. TEM analysis revealed highly dispersed Pd nanoclusters with a mean diameter of ca. 70 Å (standard deviation 14 Å) on the Pd/HT surface.

The catalytic activity of the Pd/HT for aldol reaction of ethyl cyanoacetate (**1**) with benzaldehyde (**2**) was compared with those of various solid base catalysts (Table 1). The Pd/HT as well as its precursor HT showed a high performance for the aldol reaction affording (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate (**3**) (entries 1 and 2). Other heterogeneous bases, such as Al_2O_3, MgO, $Al(OH)_3$, and $Mg(OH)_2$ were less active under the present reaction conditions (entries 3–6). After the aldol condensation using the Pd/HT, treatment with an atmospheric H_2 at 60 °C gave ethyl 2-cyano-3-phenylpropanoate (**4**) in an excellent yield. Interestingly, the catalytic activity of the Pd/HT for the hydrogenation of **3** is superior to those of commercially available Pd/carbons[13] (Scheme 1).

One-pot syntheses of various α-alkylated nitriles using carbonyl compounds were attempted in the presence of the Pd/HT catalyst, as summarized in Table 2.[14,15] A wide variety of nitriles and carbonyl compounds reacted to give excellent yields of α-alkylated nitriles; successive hydrogenation of olefinic double bonds occurred selectively leaving intact cyano, ester, amide, and sulfoxide groups (entries 1–4). On the other hand, several functional groups such as, furan ring, aromatic chloro and nitro groups, were reduced under the present alkylation reaction (entries 6, 7, and 11). α-Alkylation of malononitrile with **2** gave 2-benzylmalononitrile, a highly useful intermediate for the synthesis of α,α-dialkylated amino acids,[7b] in an 82% yield (entry 2). Furthermore, 3-phenyl-2-(2-pyridyl)propionitrile, a precursor of antiarrhythmic agents, was obtained by the Pd/HT catalyst system in a quantitative yield (entry 5), while the traditional method using benzyl chloride and a stoichiometric amount of $NaNH_2$ gave 52% yield.[16] In the reaction of an α,β-unsaturated aldehyde, no 1,4-adduct (Michael-type product) was obtained (entry 9). Although the aldol reaction of **1** with 2-thiophenecarboxaldehyde proceeded smoothly, hydrogenation of the unsaturated nitrile scarcely occurred (entry 10). The Pd/HT catalyst showed a high activity even in the presence of water: α-alkylation of **1** using aqueous 30% formaldehyde afforded ethyl 2-cyanopropionate in 91% yield (entry 12). Cyclohexanone also acted as an acceptor to yield the corresponding alkylated product (entry 14).

This Pd/HT catalyst was easily separated from the reaction mixture by a simple filtration. The recovered catalyst was washed with toluene, which could be reused with retention of its high catalytic activity and selectivity: the three recycling reactions of **1** with **2** had yields over 90%. Inductively coupled plasma analysis of the filtrate showed no leaching of the Pd species during the above reactions (detection limit 0.03 ppm).

In conclusion, we have demonstrated a multifunctional catalysis of the Pd/HT for the one-pot synthesis of α-alkylated nitriles from the reaction of various nitriles with various carbonyl compounds. This reaction system has advantages such as (i) high catalytic activity and selectivity, (ii) applicability toward diverse sets of substrates, (iii) the only byproduct is water, and (iv) simple work-up and ability to reuse of the catalyst. Heterogeneous catalysts that possess a multifunctional surface will act as pivotal tools in the development of economically and environmentally friendly chemical processes.

Acknowledgments

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12. The HT, $Mg_6Al_2(OH)_{16}CO_3$, was obtained from TOMITA Pharmaceutical Co., Ltd.
13. The Pd/carbons were purchased from N.E. Chemcat Co. Ltd (0.5 wt %) and Wako Pure Chemical Ind., Ltd (5.0 wt %).
14. In a large-scale reaction, **1** (1.70 g, 15 mmol), **2** (1.59 g, 15 mmol), the Pd/HT (0.1 wt %, 0.60 g, Pd: 0.006 mmol), and toluene (20 mL) was used. After the aldol reaction (80 °C, 3 h) and the hydrogenation (80 °C, 20 h), the catalyst was filtered and GC analysis of the filtrate showed a 97% yield of **4**. The filtrate was evaporated and the crude product was purified by distillation (180 °C/5.0 mmHg) to afford pure product (2.9 g, 95% yield, TON = 2380).
15. In the one step reaction (aldol reaction under H_2) using **1** with **2**, corresponding alkylated product (**4**) was obtained, however, the yield was low (61%, after 1 h, 80 °C) compared to that in the consecutive reaction and benzyl alcohol was formed as a byproduct.
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