

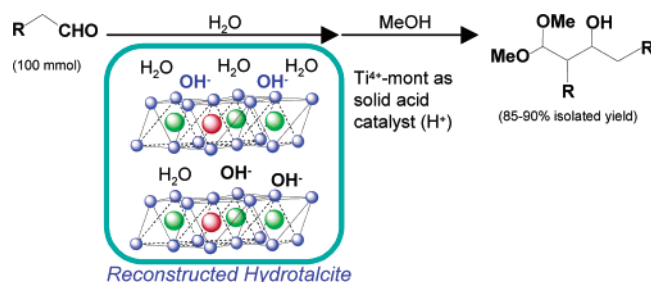
## Reconstructed Hydrotalcite as a Highly Active Heterogeneous Base Catalyst for Carbon–Carbon Bond Formations in the Presence of Water

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

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

kaneda@cheng.es.osaka-u.ac.jp

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The aldol reaction of carbonyl compounds is efficiently catalyzed by reconstructed hydrotalcites, obtained by treating the Mg–Al mixed oxide with water, as solid base catalysts in the presence of water. The catalysis of the reconstructed hydrotalcites is attributable to the surface base sites, created during the organization of the layered structure, with uniformly distributed strength. Furthermore, the reconstructed hydrotalcites provide a unique acid–base bifunctional surface capable of promoting the Knoevenagel and Michael reactions of nitriles with carbonyl compounds.

### Introduction

Solid base catalysts provide the opportunity for environmentally friendly (“green”) syntheses of fine chemicals and pharmaceuticals that conventionally involve large amounts of harmful and unrecoverable reagents such as NaOH and KOH.<sup>1–6</sup> Typical solid base catalysts, such as magnesium oxide (MgO),

possess surface O<sup>2–</sup> species as Lewis base sites.<sup>7,8</sup> The use of the solid Lewis base catalysts in large-scale syntheses is limited compared to that of solid acid catalysts because base solids are very sensitive to CO<sub>2</sub> in air to give carbonate species, which are inactive and difficult to regenerate. Few studies on solid Brønsted base catalysts have been reported despite the potential of hydroxyl anions to promote organic transformations.<sup>9</sup>

Hydrotalcites (HTs) are typical layered double-metal hydroxides consisting of alternating cationic Mg<sub>6</sub>Al<sub>2</sub>(OH)<sub>16</sub><sup>2+</sup> as the

\* To whom correspondence should be addressed. Phone and fax: +81-6-6850-6260.

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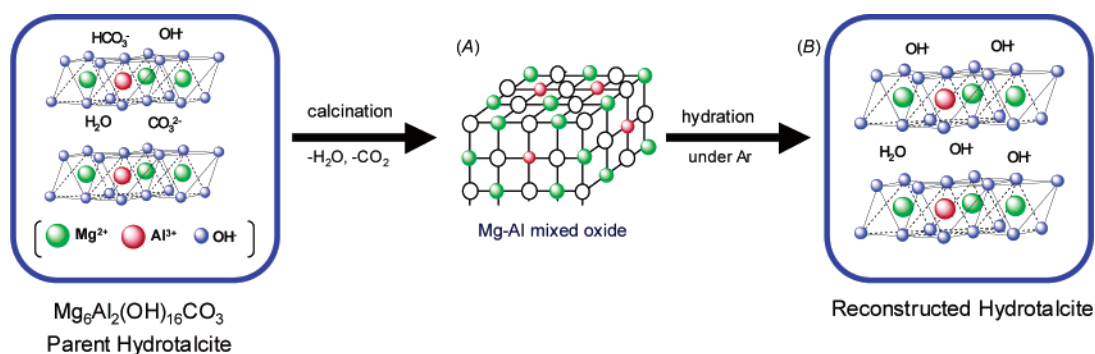
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CHART 1



brucite-like layer and anionic  $\text{CO}_3^{2-}$  interlayers.<sup>10</sup> Various heterogeneous catalysts can be developed using the unique characteristics of the HTs,<sup>11–13</sup> such as cation-exchange ability, anion-exchange ability, surface adsorption capacity, surface basicity, and reconstruction ability. For example, the HTs act as efficient solid base catalysts for a wide variety of reactions, e.g., monooxygenations using an aqueous hydrogen peroxide as an oxidant<sup>11</sup> and carbon–carbon bond formations including aldol condensation, Knoevenagel reaction, and Michael addition.<sup>13</sup>

Development of water-tolerant solid base catalysts is strongly motivated as one of the important challenges in the field of heterogeneous catalysis since water is a nontoxic and economical solvent that allows simple separation of product and the possibility of unique catalytic reactions not observed under dry conditions.<sup>14,15</sup> However, typical solid Lewis bases do not function under aqueous conditions because the surface base sites are severely poisoned by water. Here, we demonstrate a catalysis of the reconstructed HT, obtained by a regeneration of the HT structure known as the “memory effect”.<sup>10a,16,17</sup> This is the first example of a solid base catalyst capable of promoting the aldol reactions to produce  $\beta$ -hydroxy carbonyl derivatives in the

presence of water. Furthermore, this hydrotalcite catalyst system can promote the aqueous Knoevenagel and Michael reactions using nitriles. The origin and mechanism of the above unique catalysis of the reconstructed HT is discussed on the basis of the nature, strength, and amount of surface acid–base sites.

## Results

As illustrated in Chart 1, reconstructed HTs were prepared by treating Mg–Al mixed oxide in water. The surface  $\text{HCO}_3^-$  species and  $\text{CO}_3^{2-}$  anions in the interlayer of the parent HT were substituted for  $\text{OH}^-$  anions in the reconstructed form. The surface hydroxyl anion species of the reconstructed HT could act as base sites. The surface  $\text{HCO}_3^-$  and interlayer  $\text{CO}_3^{2-}$  species were removed during the calcination of the parent HTs to afford Mg–Al mixed oxides, and hydroxyl anions were incorporated into the HT structure during the organization of the layer assembly.

**Aldol Reactions Catalyzed by Reconstructed Hydrotalcites in the Presence of Water.** The aldol reaction is a cornerstone in synthetic organic chemistry to afford  $\beta$ -hydroxy carbonyls used as valuable intermediates in the synthesis of pharmacological compounds.<sup>18–20</sup> Recently, the aldol reactions of unmodified carbonyl compounds in place of preactivated enolates and enols as donors have substantially progressed using amines,<sup>18</sup> Lewis acids,<sup>21</sup> Lewis bases,<sup>22</sup> bifunctional Lewis acid/Brønsted base complexes,<sup>23,24</sup> proline as an aldolase mimic,<sup>25</sup> imidazolidinone,<sup>26</sup> and heterogeneous acid–base catalysts.<sup>13,27,28</sup> The development of solid base catalysts capable of promoting aldol

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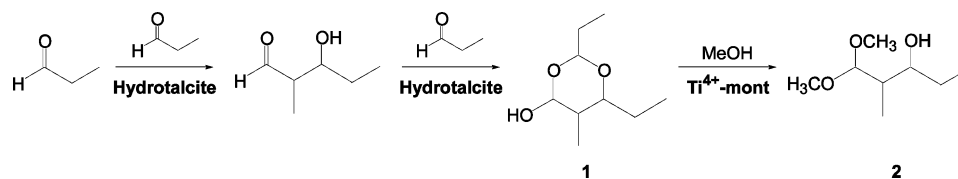
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## SCHEME 1



reactions in the presence of water remains as one of the paramount challenges in the field of organic syntheses using solid catalysts.<sup>15,29</sup> The aldol reaction under aqueous conditions can be expected to give a favorable situation which can prevent dehydration of  $\beta$ -hydroxy aldehydes into the corresponding enones with respect to equilibrium issues. We found that the reconstructed HT acted as an efficient heterogeneous base catalyst for the aldol reaction of aldehydes in the presence of water.

Initial investigations revealed that the reconstructed HT with a Mg/Al ratio of 3 promoted the aldol coupling of propionaldehyde at room temperature to provide hemiacetal **1**.<sup>26</sup> The formation of hemiacetal **1** was confirmed by <sup>1</sup>H NMR analysis of crude reaction mixtures. The hemiacetal was unstable during the analyses using GC and GC–MS; however, methanolysis of this hemiacetal in the presence of methanol using a Ti<sup>4+</sup>-mont as a solid acid catalyst allows direct access to the 1,1-dimethoxy-2-methyl-3-pentanol as a stable  $\beta$ -hydroxy dimethylacetal, **2** (Scheme 1).<sup>30,31</sup>

As shown in Table 1, the reconstructed HT gave the dimethylacetal in 85% yield within 1 h in the presence of water used for the reconstruction of the HT (entry 1). With respect to cosolvents, water was a good cosolvent to give the  $\beta$ -hydroxy dimethylacetal in 70% yield (entry 2).<sup>32</sup> The use of toluene and *n*-heptane gave an aqueous/organic biphasic system in which the HT catalyst was present in the aqueous phase, affording 82% and 76% yields of **2**, respectively (entries 3 and 4). THF and DMF also gave good yields of the corresponding product (entries 5 and 6), while dichloromethane was significantly less effective (entry 7).

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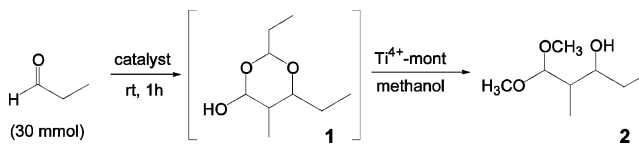
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(31) Treatment of 1,1-dimethoxy-2-methylpentan-3-ol (**2**) with water in the presence of the Ti<sup>4+</sup>-mont catalyst exclusively afforded 3-hydroxy-2-methylpentanal as an aldol product of propionaldehyde.

(32) The amount of water as a solvent is a crucial factor for the catalytic activity of the reconstructed HT. The yield of **2** gradually decreased with increasing amount of water: 78% (1 mL), 70% (2 mL), and 25% (3 mL).

TABLE 1. Aldol Reaction of Propionaldehyde Using Various Catalysts and Subsequent Methanolysis<sup>a</sup>



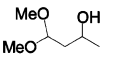

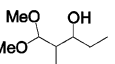

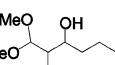
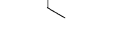


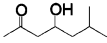


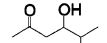


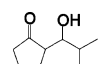


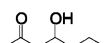
entry	catalyst	cosolvent	yield <sup>b</sup> (%)
1	reconstructed HT (Mg/Al = 3)		85
2	reconstructed HT (Mg/Al = 3)	water	70
3	reconstructed HT (Mg/Al = 3)	toluene	82
4	reconstructed HT (Mg/Al = 3)	<i>n</i> -heptane	76
5	reconstructed HT (Mg/Al = 3)	THF	80
6	reconstructed HT (Mg/Al = 3)	DMF	75
7	reconstructed HT (Mg/Al = 3)	CH <sub>2</sub> Cl <sub>2</sub>	39
8 <sup>c</sup>	reconstructed HT (Mg/Al = 3)		65
9	reconstructed HT (Mg/Al = 4)		74
10	reconstructed HT (Mg/Al = 5)		47
11	reconstructed HT (Mg/Al = 2)		34
12	untreated HT (Mg/Al = 3)		0
13 <sup>d</sup>	MgO		0
14 <sup>e</sup>	Mg(OH) <sub>2</sub>		0
15 <sup>f</sup>	Mg(OH) <sub>2</sub> + Al(OH) <sub>3</sub>		0
16 <sup>g</sup>	Na <sub>2</sub> CO <sub>3</sub>		0
17 <sup>g</sup>	NaHCO <sub>3</sub>		0
18 <sup>g</sup>	CaCl <sub>2</sub>		0
19 <sup>g</sup>	NaOH		3 <sup>h</sup>

<sup>a</sup> Reaction conditions: aldol reaction, propionaldehyde (30 mmol, 2.4 mL), water (1 mL), cosolvent (2 mL), HT (0.15 g), rt, 1 h; methanolysis, MeOH (50 mL), Ti<sup>4+</sup>-mont (0.45 g), rt, 4 h. <sup>b</sup> The yield and selectivity to 1,1-dimethoxy-2-methylpentan-3-ol were determined by GC using an internal standard method. <sup>c</sup> The reconstructed HT was degassed at 100 °C before use. <sup>d</sup> MgO (0.2 g) was used. <sup>e</sup> Mg(OH)<sub>2</sub> (0.2 g) was used. <sup>f</sup> A physical mixture of Mg(OH)<sub>2</sub> (0.026 g, 0.45 mmol) and Al(OH)<sub>3</sub> (0.012 g, 0.15 mmol) was used. <sup>g</sup> Five millimoles of catalyst was used. <sup>h</sup> (*E*)-2-Methyl-2-pentenal was formed as the main product in 95% yield.

Table 1 also compares the catalytic activity of the reconstructed HT for the aldol reaction of propionaldehyde with those of various homogeneous and heterogeneous catalysts under aqueous conditions, e.g., without cosolvent. The reconstructed HT with a Mg/Al ratio of 3 gave the highest yield of **2** (entry 1 vs entries 9–19). The parent HT and Mg(OH)<sub>2</sub> as well as a physical mixture of Mg(OH)<sub>2</sub> and Al(OH)<sub>3</sub> were inactive (entries 12, 14, and 15). MgO as a typical solid Lewis base<sup>3</sup> did not show any catalytic activity (entry 13), and conventional base compounds such as Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, and CaCl<sub>2</sub><sup>22b</sup> also were inactive (entries 16–18). In contrast, NaOH, as a water-soluble strong base, effectively catalyzed the aldol reaction to give (*E*)-2-methyl-2-pentenal in 95% yield as a dehydration product of 2-methyl-3-hydroxypentanal (entry 19). When the reconstructed HT was degassed at 100 °C before use, the yield of **2** was depressed to 65% even in the presence of water (entry 1 vs entry 8).

As summarized in Table 2, the reconstructed HT could also promote a 100 mmol scale self-aldol reaction of various aliphatic aldehydes. For example, 5.8 g (100 mmol) of propionaldehyde was converted efficiently with 0.15 g of reconstructed HT within

TABLE 2. Aldol Reactions of Aldehydes Catalyzed by Reconstructed Hydrotalcite<sup>a</sup>

entry	donor	acceptor	product	time (h)	yield (%) <sup>b</sup>
1	CH <sub>3</sub> CHO			2	85
2				1	89
3 <sup>c</sup>				2	90
4				2	8 <sup>d</sup>
5 <sup>e</sup>				1	67
6 <sup>e</sup>				10	78
7 <sup>e</sup>				7	68 <sup>f</sup>
8 <sup>f</sup>				13	70

<sup>a</sup> Reaction conditions: substrate (100 mmol), water (1 mL), HT (0.15 g), rt. <sup>b</sup> Isolated yields. For self-aldol reactions, the isolated yields of the corresponding  $\beta$ -hydroxy dimethoxyacetals are shown. <sup>c</sup> A 0.1 mol % concentration of DTMAB was added. <sup>d</sup> GC yield. <sup>e</sup> Donor (20 mmol), acceptor (10 mmol), water (0.3 mL). <sup>f</sup> Donor (100 mmol), acceptor (10 mmol), water (0.5 mL). *n*-Butylaldehyde was added stepwise into the reaction mixture. See the Experimental Section for details. <sup>g</sup> Only the *syn* product was isolated, determined by <sup>1</sup>H NMR.

1 h to afford **2** in 89% isolated yield (entry 2). As the hydrophilic reconstructed HTs existed in the aqueous phase,<sup>11</sup> water-insoluble aldehyde such as *n*-butylaldehyde resulted in a low yield (entry 4). Addition of a cationic surfactant, i.e., *n*-dodecyltrimethylammonium bromide (DTMAB), however, could accelerate the aldol reaction of *n*-butylaldehyde to give a 90% yield of the corresponding product within 2 h (entry 3).<sup>33</sup>

Furthermore, this catalyst system is extended to the cross-aldol reaction with aliphatic aldehydes using excess ketones to avoid self-aldolization of the aldehyde. The results are also included in Table 2. Acetone reacted with isovaleraldehyde to give 4-hydroxy-6-methyl-2-heptanone in 67% yield for 1 h (entry 5). The  $\alpha$ -substituted aldehydes required a longer reaction time; the reaction of acetone with isobutyraldehyde produced 4-hydroxy-5-methyl-2-hexanone in 78% yield in 10 h (entry 6). In the reaction of acetone with *n*-butylaldehyde, homodimerization of *n*-butylaldehyde prevailed over the cross-aldol reaction, but a stepwise addition of *n*-butylaldehyde into acetone suppressed the homocoupling of *n*-butylaldehyde, thus giving 4-hydroxy-2-heptanone as the cross-aldol product in good yield (entry 8).

The solid catalyst was removed by filtration from the reaction mixture at about 50% conversion of propionaldehyde under an Ar atmosphere, and then further treatment of the colorless filtrate at room temperature for 5 h did not give any additional products. Furthermore, the spent HT catalyst could be reused once with

(33) In the 100 mmol scale aldol reaction of *n*-butylaldehyde using the reconstructed HT, the following reactivity of surfactants was observed: DTMAB (90) > sodium dodecyl sulfate (35) > Triton X 100 (13) > non (8). The values in parentheses are yields of 1,1-dimethoxy-2-ethyl-3-hexanol. Without the reconstructed HT catalyst, the aldolization did not occur even in the presence of DTMAB.

retention of its high activity and selectivity; the yield of **2** in the reaction of propionaldehyde remained greater than 80% during the recycling experiment. These aldol reactions clearly occurred on the surface of the reconstructed hydrotalcite.

This is the first example of aldol reactions to produce  $\beta$ -hydroxy carbonyl compounds catalyzed by the reconstructed hydrotalcites.

**Reactions of Nitriles by Reconstructed Hydrotalcite Catalyst in the Presence of Water.** The reconstructed HT was applied to other carbon–carbon bond formations such as the Knoevenagel and Michael reactions<sup>34,35</sup> using nitriles in the presence of water.

In the presence of the reconstructed HT catalyst, the Knoevenagel reaction of an equimolar mixture of malononitrile ( $pK_a = 11.2$ )<sup>36</sup> with benzaldehyde afforded benzylidenemalononitrile in 96% yield in 1 h,<sup>37</sup> and ethyl cyanoacetate ( $pK_a = 9.0$ ) also gave (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate in 94% yield, whereas this reaction required 10 h to attain quantitative yield (Table 3, entries 11 and 12).

Furthermore, the reconstructed HT catalyst smoothly promoted the Knoevenagel reaction of activated nitriles such as 2-cyanoacetamide and 2-pyridineacetonitrile in DMF as a water-miscible solvent, as shown in Table 3 (entries 9 and 10). Surprisingly, the Knoevenagel reaction of phenylacetonitrile with a large  $pK_a$  value of 21.9<sup>36</sup> proceeded efficiently in the presence of the reconstructed HT catalyst, whereas RuH<sub>2</sub>(PPh<sub>3</sub>)<sub>4</sub> as a typical metal complex for the reaction of nitriles<sup>38</sup> could not efficiently catalyze the above reaction using phenylacetonitrile. The representative results with phenylacetonitrile are also included in Table 3.<sup>39</sup> Reactions with benzaldehyde and 2-furancarboxaldehyde afforded (*Z*)-1,2-diphenylethylidenenitrile and (*Z*)-2-furanylmethylenebenzeneacetonitrile in 1 h, respectively (entries 1 and 3). Aliphatic aldehydes of *n*-octanaldehyde, isobutyraldehyde, and cyclohexanecarboxaldehyde gave the corresponding condensation products in high yields (entries 4–6). The reaction of phenylacetonitrile with unsaturated aldehyde such as cinnamaldehyde exclusively gave the corresponding nitrile as a 1,2-addition product with retention of the double bond configuration (entry 7).<sup>13b,40</sup> The reaction of an aliphatic nitrile, e.g., *n*-octanenitrile with benzaldehyde did not yield any products.

In the reaction of phenylacetonitrile with enones, 1,4-addition occurred exclusively to give the corresponding Michael adducts, as summarized in Table 4.<sup>41,42</sup> For example, phenylacetonitrile

(34) Jones, G. *Org. React.* **1967**, *15*, 204.

(35) (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4. (c) Ho, T.-L. *Tactics of Organic Synthesis*; Wiley: New York, 1994.

(36) (a) Martell, A. E.; Smith, R. M. In *Critical Stability Constants*; Plenum Press: New York, 1974, 1975, 1977; Vols. 1–3. (b) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439. (c) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(37) The Knoevenagel reaction of malononitrile with benzaldehyde without any catalyst in the presence of water has been reported. See: Bigi, F.; Conforti, M. L.; Maggi, R.; Piccinno, A.; Sartori, G. *Green Chem.* **2000**, *2*, 101. Under our reaction conditions, the reaction of malononitrile with benzaldehyde gave 82% of the corresponding product.

(38) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiyama, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436.

(39) An excess acceptor was used to avoid the Michael reaction.

(40) Cabello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. *J. Org. Chem.* **1984**, *49*, 5195.

(41) Ethyl cyanoacetate also reacted with 2-cyclohexen-1-one to afford the 1,4-addition product selectively. However, the yield of the Michael product was lower than 50%.

**TABLE 3.** Knoevenagel Reaction of Nitriles with Various Carbonyl Compounds<sup>a</sup>

		$R_1\text{-CN} + R_2\text{-CHO} \xrightarrow[\text{H}_2\text{O, DMF}]{\text{reconstructed HT (Mg/Al=3)}} R_2\text{-CH=C(R}_1\text{)-CN}$			
entry	donor	acceptor	product	time (h)	yield (%) <sup>b</sup>
1				1	98 (81)
2 <sup>c</sup>				1	9
3				1	quant. (96)
4 <sup>d</sup>				10	quant. (80)
5				24	90 (86)
6				24	77 (70)
7 <sup>d</sup>				3	78 (70)
		<i>E/Z=2/3</i>	<i>E/Z=2/3</i>		
8 <sup>d,e</sup>				4	76 (70)
9				1	97 (93)
10				1	98 (95)
11 <sup>f,g</sup>				1	96 (91)
12 <sup>f</sup>				10	94 (90)

<sup>a</sup> Reaction conditions: donor (3 mmol), acceptor (6 mmol), water (0.3 mL), DMF (2 mL), HT (0.15 g), 80 °C. <sup>b</sup> Determined by GC using an internal standard method. Values in parentheses are isolated yields. <sup>c</sup> Diethylamine (4 mmol) was used as a catalyst. <sup>d</sup> 1,4-Dioxane (2 mL) was used as a cosolvent. <sup>e</sup> At 40 °C, donor (1 mmol), acceptor (3 mmol). <sup>f</sup> Donor (10 mmol), acceptor (10 mmol), water (1 mL), 60 °C. <sup>g</sup> The corresponding coupling product was obtained in 82% yield in the absence of the reconstructed hydrotalcite catalyst.

reacted with 2-cyclohexen-1-one, affording  $\alpha$ -(3-oxocyclohexyl)-phenylacetonitrile in high yield without formation of a 1,2-addition product (entry 1). The reaction with 3-nonen-2-one, benzalacetone, and cinnamaldehyde as acceptors gave the Michael products in high yields; however, the reaction required prolonged reaction times (entries 2–4). Furthermore, a bulky nitrile such as 1-naphthylacetonitrile could be used as a donor to produce  $\alpha$ -(3-oxocyclohexyl)-1-naphthylacetonitrile in high yield (Scheme 2).

The reaction of 2,4-pentanedione, which has a  $pK_a$  (9.0) similar to that of ethyl cyanoacetate,<sup>36</sup> with benzaldehyde did not afford any products. In contrast, the same reaction using KOH as a homogeneous Brønsted base gave a mixture of 3-benzylidene-2,4-pentanedione and benzalacetone.<sup>43</sup> The Michael reaction of ethyl acetoacetate with 3-buten-2-one or methyl acrylate proceeded, but required prolonged reaction times (Scheme 3).

Conclusively, the reconstructed hydrotalcite is an efficient heterogeneous catalyst for the carbon–carbon bond forming

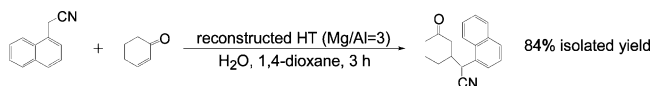
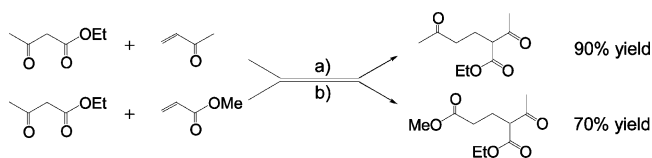
(42) Michael reaction of nitriles using a homogeneous catalytic system. See: (a) (CsF/Si(OR)<sub>4</sub>) Boyer, J.; Corriu, R. J. P.; Reye, R. P. et al. *Tetrahedron* **1983**, 39, 117. (b) (NaOH/calix[n]arenes) Shimizu, S.; Shirakawa, S.; Suzuki, T.; Sasaki, Y. *Tetrahedron* **2001**, 57, 6169.

(43) Benzalacetone is formed by base-catalyzed condensation of 2,4-pentanedione with benzaldehyde followed by decylation. See: Tsuboi, S.; Uno, T.; Takeda, A. *Chem. Lett.* **1978**, 1325.

**TABLE 4.** Reconstructed Hydrotalcite-Catalyzed Michael Reaction of Nitriles with  $\alpha,\beta$ -Unsaturated Compounds<sup>a</sup>

		$R_1\text{-CN} + R_2\text{-CH=CH-E} \xrightarrow[\text{H}_2\text{O, 1,4-dioxane}]{\text{reconstructed HT (Mg/Al=3)}} R_1\text{-CH=C(R}_2\text{)-CH}_2\text{-E}$			
entry	donor	acceptor	product	time (h)	yield (%) <sup>b</sup>
1				1.5	97 (80)
2				10	85 (83)
3				12	quant. (95)
4				12	85 (75)

<sup>a</sup> Reaction conditions: donor (6 mmol), acceptor (3 mmol), water (0.3 mL), 1,4-dioxane (2 mL), HT (0.15 g), 80 °C. <sup>b</sup> Yields were based on the acceptor and were determined by GC using an internal standard method. Values in parentheses are isolated yields.

**SCHEME 2****SCHEME 3<sup>a</sup>**

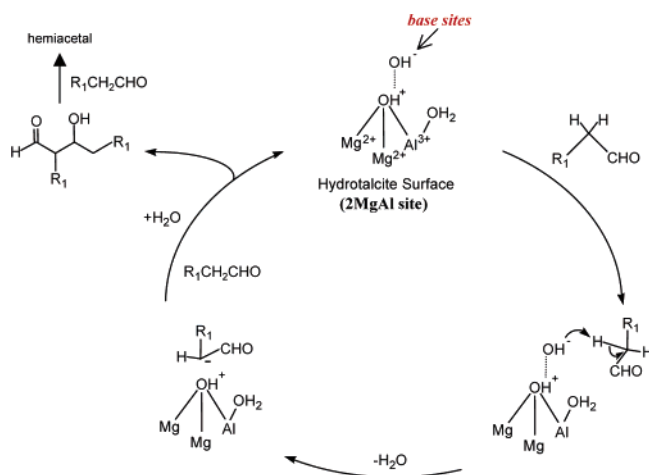
<sup>a</sup> Reagents and conditions: (a) donor (10 mmol), acceptor (8 mmol), water (2 mL), acetone (2 mL), HT (0.30 g), 60 °C, 48 h; (b) donor (5 mmol), acceptor (5 mmol), water (1 mL), THF (4 mL), HT (0.15 g), 30 °C, 24 h.

reactions of various unmodified carbonyl compounds and nitriles in the presence of water. Nitriles are good donors rather than 1,3-dicarbonyl compounds for the carbon–carbon bond forming reactions catalyzed by reconstructed HT. The above specific reactivity will be discussed in the next section.

**Discussion**

The reconstructed hydrotalcite described here provides the first example of the aldol reaction of aliphatic aldehydes in the presence of water, which is in sharp contrast to the HT catalysts pioneered by Figueras et al.<sup>13</sup> The significant difference between two HT catalysts arises from their preparation procedures<sup>17</sup> as well as the target reaction and the amount of water used as a solvent. Figueras et al. prepared HTs by treating the Mg–Al mixed oxide with water, followed by their use as catalysts after treatment under a vacuum to remove the water for the aldol reaction of acetone and benzaldehyde in 12 mL of water.<sup>13e</sup> In contrast, the present reconstructed HTs were synthesized by hydration of the Mg–Al mixed oxides and then subjected to the aldol reactions of aliphatic aldehydes in 1 mL of water without the above evacuation of the water-covered HTs. We found that the drying treatment of the hydrated HTs and the amount of water definitely influenced the catalytic activity for

## SCHEME 4



the aldol reaction of aliphatic aldehydes.<sup>44</sup> The yield of the product in the reaction of propionaldehyde was depressed even in the presence of water once the reconstructed HTs were dried under a vacuum (Table 1, entry 8). Furthermore, the yield of **2** gradually decreased with increasing amount of water.<sup>32</sup> Presumably, the small amount of water maintains the hydroxyl groups as base sites on the surface of the reconstructed hydrotalcites, while the generated  $\text{OH}^-$  species were weakly adsorbed on the surface of the HT, and therefore were easily removed as  $\text{H}_2\text{O}$  by the evacuation. The elimination of adsorbed water might result in the formation of  $\text{O}^{2-}$  species as Lewis base sites that are easily poisoned by water.

In the following, the strength and amount of base sites in our reconstructed HTs are discussed to elucidate the origin of their remarkable catalyses for the aldol reaction of aldehydes and the reactions with nitriles.

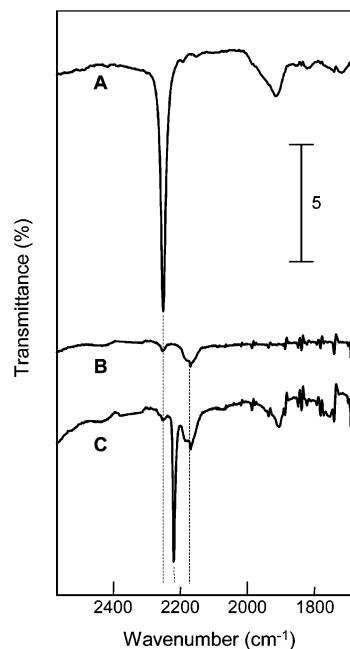
#### Surface Basicity of Reconstructed Hydrotalcite Catalyst.

We found that the rate of the aldol reaction of *n*-butyraldehyde was sensitive to the  $\text{p}K_{\text{a}}$  of amines. Use of diethylamine ( $\text{p}K_{\text{a}} = 10.98$ )<sup>36</sup> and piperidine ( $\text{p}K_{\text{a}} = 11.2$ ) gave 1,1-dimethoxy-2-ethylhexan-3-ol as the corresponding aldol product in 92% and 80% yield for 3 h, respectively, whereas the reaction did not take place with triethylamine ( $\text{p}K_{\text{a}} = 10.72$ ). Therefore, it might be said that the base strength of the reconstructed HTs in the presence of water may exist within a very narrow  $\text{p}K_{\text{a}}$  range of 10.72–11.2. Figueras et al. and Corma et al. have independently reported that the HTs had base sites with a  $\text{p}K_{\text{a}}$  value of at least 11 by comparing the activities of HTs with those of amines.<sup>13a,45</sup>

The base amount of the HT catalyst is estimated by titration using benzoic acid ( $\text{p}K_{\text{a}} = 4.2$ ) as a titer in the Michael reaction of ethyl acetoacetate with methyl acrylate in the presence of water (Scheme 3b), which was chosen as the test reaction to compare the catalytic activities between the reconstructed and parent HTs under identical conditions. The catalytic activity of

(44) Recently, Medina et al. have reported the structure and catalysis of hydrated HTs prepared by different procedures in the liquid or gas phase. See ref 17a. Despite the marked difference in catalytic activity between two reconstructed HTs in the aldol condensation of citral with acetone, the number and nature of  $\text{OH}^-$  groups are indistinguishable. We think that the identical basicity of the HTs prepared by different methods may arise from the evacuation and/or exposure of the hydrated HTs to air before the condensation reaction.

(45) Corma, A.; Fornés, V.; Martín-Aranda, R. M.; Rey, F. *J. Catal.* **1992**, *134*, 58.



**FIGURE 1.** IR spectra of (A) phenylacetonitrile, (B) adsorbed phenylacetonitrile on reconstructed hydrotalcite, and (C) the phenylacetonitrile from (B) after the reaction with benzaldehyde. Note that spectrum C is identical to that of (*Z*)-1,2-diphenylethylenitrile as the product of the Knoevenagel reaction of phenylacetonitrile with benzaldehyde.

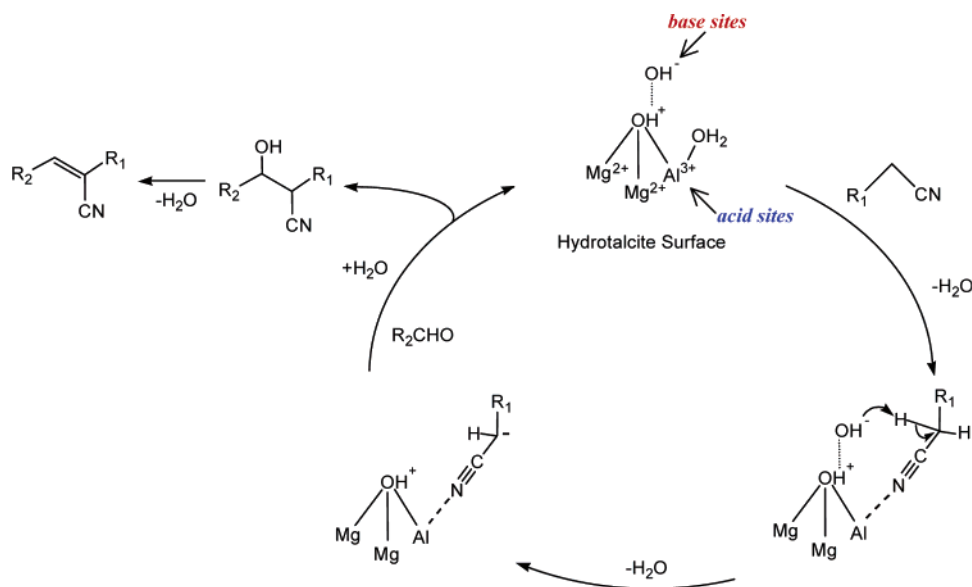
the parent HT for this Michael reaction was 10-fold less than that of the reconstructed HT. The titer to diminish the catalytic activity is a measure of the effective base amount. The base amount of the reconstructed HT ( $\text{Mg}/\text{Al} = 3$ ) was approximately  $4.0 \text{ mmol}\cdot\text{g}^{-1}$ , which is larger than that of the untreated HT ( $0.7 \text{ mmol}\cdot\text{g}^{-1}$ ). The latter is associated with anionic species such as  $\text{HCO}_3^-$ , which compensate for the positive charge of the Brucite-like layer. Increasing the  $\text{Mg}/\text{Al}$  ratio from 3 to 5 decreased the base amount ( $2.6 \text{ mmol}\cdot\text{g}^{-1}$ ), which well correlates with the catalytic activity in the aldol reaction of propionaldehyde (Table 1, entry 1 vs entry 10). The turnover number (TON) normalized to the above base amount of the reconstructed HT ( $\text{Mg}/\text{Al} = 3$ ) was 150. It is notable that this TON value is significantly larger than those for the imidazolidinone, e.g.,  $\text{TON} \approx 9$ ,<sup>26</sup> and L-proline, e.g.,  $\text{TON} \approx 8$ , which is an efficient organocatalyst for the aldol reaction.<sup>25d</sup>

#### Reaction Mechanism. (A) Aldol Reaction of Carbonyl Compounds.

A proposed mechanism is shown in Scheme 4 where the above surface  $\text{OH}^-$  species of the reconstructed HT efficiently acts as a Brønsted base site in the presence of water. The surface  $\text{OH}^-$  species abstracts an acidic hydrogen of aldehyde as a pronucleophile in the aqueous phase to generate a carbanion intermediate, which can be paired with the cationic surface of the hydrotalcite. The tuned base strength between 10.72 and 11.2 on the  $\text{p}K_{\text{a}}$  scale depressed the dehydration of the aldol products, leading to high selectivity for the putative 3-hydroxy aldehydes. 3-Hydroxy aldehydes are reacted with another aldehyde to afford the corresponding hemiacetal compounds by a base-catalyzed mechanism.<sup>26</sup>

The surface of the reconstructed HT in the aqueous phase provides a highly hydrophilic environment for the above aldol reaction. Therefore, the reaction of hydrophilic aldehydes such as propionaldehyde efficiently proceeded on the polar surface of the reconstructed HT in the aqueous phase. The reaction of

## SCHEME 5



a hydrophobic aldehyde such as *n*-butyraldehyde requires DTMAB as a cationic surfactant (vide supra). Under these phase-transfer conditions,<sup>11b</sup> the surface hydroxyl anion species interacts with quaternary ammonium cation ( $Q^+$ ) and then passes into the organic phase by forming an ion pair such as a  $Q^+OH^-$  species to react with a lipophilic aldehyde substrate at the interface as a reaction zone.

**(B) Reactions of Nitriles.** In contrast to the aldol reaction of *n*-butyraldehyde, diethylamine hardly promoted the reaction of phenylacetonitrile with benzaldehyde (Table 3, entry 2). Furthermore, the reactivity of the donors was not associated with their  $pK_a$  values. For example, ethyl cyanoacetate showed a significantly low reactivity compared with malononitrile ( $pK_a = 11.2$ ) despite having a lower  $pK_a$  value of 9.0 (Table 3, entry 11 vs entry 12).<sup>46</sup> Therefore, the catalysis of the reconstructed HT in the Knoevenagel reaction cannot be explained in terms of the surface basicity alone.

As shown in Figure 1B, the  $\nu(CN)$  band of phenylacetonitrile adsorbed onto the reconstructed HT appeared at  $2170\text{ cm}^{-1}$ , which is lower than that of the free phenylacetonitrile ( $2253\text{ cm}^{-1}$ ). This peak is assignable to an  $[Al]^{+}[PhCHCN]^{-}$  species<sup>47</sup> and clearly demonstrates the coordination of the nitrile with the Lewis acid center of the reconstructed HT surface. The shift of  $\nu(CN)$  observed for the reconstructed HT of  $83\text{ cm}^{-1}$  is smaller than that for the cationic RuHAP catalyst using ethyl cyanoacetate.<sup>29</sup> The surface Lewis acid sites of reconstructed HTs, e.g., Al cations, react with nitriles, which increases the acidity of the  $\alpha$ -hydrogens of the nitriles in a fashion similar to that of the Ru-catalyzed reaction of nitriles.<sup>29,38</sup> A possible reaction mechanism via coordination of nitriles is illustrated in Scheme 5.

The initial step in the mechanism is a coordination of the cyano group to the Al cation as a Lewis acid site, which increases the acidity of the  $\alpha$ -hydrogen of the nitrile. A neighboring base site of hydroxyl anion abstracts the  $\alpha$ -hydrogen to form an ion pair of the carbanion species and Al cation,

followed by a coupling reaction with a carbonyl compound to yield the  $\alpha,\beta$ -unsaturated nitrile and  $H_2O$ . The Hammett  $\rho$  value in the Knoevenagel reaction of *para*-substituted phenylacetonitrile and benzaldehyde catalyzed by reconstructed HT is 2.3, which is larger than 0.97 using KOH. This indicates a formation of highly polar intermediates on the surface of the reconstructed HT.

The Lewis acid site of the reconstructed HT also initiates the reaction of phenylacetonitrile with enones by the coordination of the nitrile to afford the 1,4-addition product exclusively. The same regioselectivity toward the 1,4-addition has been observed for the reaction using homogeneous and heterogeneous catalytic systems.<sup>3a,41</sup>

## Conclusions

The present preparation method, which utilizes the facile structural change of HTs, could be a powerful protocol for the immobilization of hydroxyl groups on the HT surface for use as hydrophilic heterogeneous base catalysts for selective carbon–carbon bond forming reactions in the presence of water. Furthermore, the reconstructed hydroxalcite possesses a highly effective acid–base bifunctional surface capable of mediating the Knoevenagel and Michael reactions of nitriles with carbonyl compounds. Our strategy to design a highly functionalized metal hydroxide surface without any transition and rare earth metals offers the possibility of performing diverse and environmentally benign carbon–carbon bond forming reactions.

## Experimental Section

**Preparation of Reconstructed Hydroxalcite.** A 0.15 g sample of the above HT was placed in a Pyrex glass reactor (30 mm i.d.) and then heated at  $450\text{ }^\circ\text{C}$  for 7 h in a continuous Ar flow. After the sample was cooled in the Ar flow, decarbonated water, typically 1 mL, was poured onto the sample, followed by stirring at room temperature for 8 h, giving a reconstructed HT. The elemental analysis of the solid demonstrated retention of the initial Mg/Al ratio. Retention of the Mg/Al ratio in the reconstructed HT samples also was confirmed by the EDX (energy-dispersive X-ray) measurement of the powder.

**Aldol Reaction of Aldehydes.** A typical example for the HT-catalyzed aldol reaction of aldehyde is as follows. Onto the wet

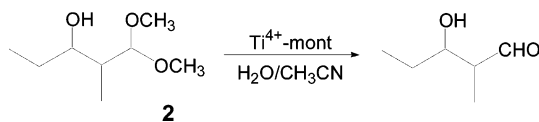
(46) The same phenomenon has been reported for the Knoevenagel condensation of methylene compounds with benzaldehyde catalyzed by the CsX zeolite as a solid Lewis base.<sup>2c</sup>

(47) Pasynkiewicz, S.; Starowieyski, K.; Rzepkowska, Z. *J. Organomet. Chem.* **1967**, *10*, 527.

reconstructed HT (0.15 g) was added the freshly distilled propionaldehyde (5.8 g, 100 mmol). After the heterogeneous mixture was stirred at room temperature for 1 h under an Ar atmosphere, the HT catalyst was separated by filtration. *All procedures must be operated under an Ar atmosphere to avoid adsorption of carbon dioxide on the surface.* After treatment of the collected filtrate with MgSO<sub>4</sub> and concentration in vacuo, methanol (50 mL) and Ti<sup>4+</sup>-mont (0.45 g) as a solid acid catalyst<sup>30</sup> were added. The heterogeneous solution was stirred at room temperature until the reaction was judged complete by GC analysis (4 h). The Ti<sup>4+</sup>-mont was removed by filtration, and the filtrate was concentrated in vacuo. Column chromatography on Florisil with a mixture of *n*-hexane and ethyl acetate (9/1) afforded 4.93 g of pure 1,1-dimethoxy-2-methyl-3-pentanol (89% yield).

The HT-mediated aldol reaction of *n*-butyraldehyde (100 mmol) was performed in the presence of water (1 mL) and 0.1 mmol of *n*-dodecyltrimethylammonium bromide at room temperature for 2 h. After the methanolysis of the hemiacetal according to the procedure described above, column chromatography on Florisil with a mixture of *n*-hexane and ethyl acetate afforded 5.69 g of pure 1,1-dimethoxy-2-ethyl-3-hexanol (90% yield).

**Deprotection of 1,1-Dimethoxy-2-methylpentan-3-ol.** To the reaction vessel containing Ti<sup>4+</sup>-mont (0.2 g) were successively added CH<sub>3</sub>CN (25 mL), H<sub>2</sub>O (5 mL), and 1,1-dimethoxy-2-methylpentan-3-ol (**2**) (1 g, 6.2 mmol). After the heterogeneous reaction mixture was stirred at 55 °C for 1 h, Ti<sup>4+</sup>-mont was removed by filtration. The filtrate was concentrated to about 15 mL under vacuum at room temperature. The residue was extracted with ether, and then the organic layer was dried with MgSO<sub>4</sub> and carefully concentrated in an ice–water bath to avoid acetalization of the aldol. The NMR analysis showed a complete conversion of **2** into 3-hydroxy-2-methylpentanal without formation of 2-methyl-2-pentenal and the acetal of the aldol.



**Reuse of the Catalyst.** The spent HT was washed with acetone, followed by heating at 450 °C and treated with water again. Then the HT catalyst was recyclable once without losing high selectivity in the aldol reaction of propionaldehyde.

**Cross-Aldol Reaction of Ketones with Aldehydes.** A typical example is for cross-aldolization of acetone and *n*-butyraldehyde. *n*-Butyraldehyde (10 mmol) was successively added (2.5 mmol × 4 in 1 h) onto a heterogeneous mixture of acetone (100 mmol) and reconstructed HT (0.15 g) with 0.5 mL of decarbonated water. The mixture was stirred at room temperature for 13 h, and then the solid catalyst was removed by filtration. The GC analysis of the filtrate showed a 75% yield of 4-hydroxy-2-heptanone, based on *n*-butyraldehyde, as a cross-coupling product. The filtrate was concentrated in vacuo, and column chromatography on silica gel (WAKO gel C-200) with a mixture of *n*-hexane and ethyl acetate (4/1) afforded 1.1 g of pure 4-hydroxy-2-heptanone (70% yield).

**Knoevenagel Reaction of Nitriles with Carbonyl Compounds.** A typical example is as follows. To the reaction vessel containing

the reconstructed HT and water (0.3 mL) were successively added DMF (2 mL), phenylacetonitrile (3 mmol), and benzaldehyde (6 mmol). After the reaction mixture was stirred at 80 °C for 1 h, the HT was separated by filtration. GC analysis showed a 98% yield of (*Z*)-1,2-diphenylethylidenenitrile. The filtrate was collected and subjected to column chromatography on the silica gel with a mixture of *n*-hexane and ethyl acetate (4/1) to afford 0.50 g of pure (*Z*)-1,2-diphenylethylidenenitrile (81% yield).

**Titration of the Catalytic Activity of Hydrotalcites.** To the reaction vessel containing the reconstructed HT and water (1 mL) were successively added THF (4 mL), an appropriate amount of benzoic acid, ethyl acetoacetate (5 mmol), and methyl acrylate (5 mmol). After the reaction mixture was stirred at 30 °C for 12 h, the HT catalyst was separated by filtration. The filtrate was subjected to GC analysis to determine the amount of the corresponding Michael adduct 2-acetylpentanedioic acid 1-ethyl 5-methyl diester. The amount of benzoic acid necessary to diminish the catalytic activity is defined as the amount of base sites of the surface.

**IR Measurement.** The IR spectra of the reconstructed HT were obtained at room temperature in transmission mode. The reconstructed HT (0.15 g) was treated with 1 mmol of phenylacetonitrile at 80 °C for 15 min in the presence of water (0.3 mL). Subsequently, 2 mmol of benzaldehyde was added to the heterogeneous reaction mixture. In each step, the solid was pressed into a disk with KBr after removal of solvent by evaporation and subjected to IR measurement. Treatment of the adsorbed phenylacetonitrile on the HT surface with benzaldehyde afforded an IR peak at 2218 cm<sup>-1</sup> (Figure 1C), which is identical to that of (*Z*)-1,2-diphenylethylidenenitrile as the product (2219 cm<sup>-1</sup>).

**Hammett Plot.** The Hammett plots for the Knoevenagel reaction of *para*-substituted phenylacetonitriles (X = OCH<sub>3</sub> and Cl) with benzaldehyde were obtained in a competitive reaction. The heterogeneous mixture of reconstructed HT (0.05 g), *para*-substituted phenylacetonitrile (5 mmol), phenylacetonitrile (5 mmol), benzaldehyde (5 mmol), water (0.1 mL), and 1,4-dioxane (5 mL) was stirred at 80 °C for 30 min. The KOH-promoted Knoevenagel reaction was performed using 0.3 mmol of KOH for 5 min.

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**Supporting Information Available:** General procedure, characterizations of products and reconstructed hydrotalcite, XRD, Hammett plot, and discussion on the location of base sites on the hydrotalcite surface (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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