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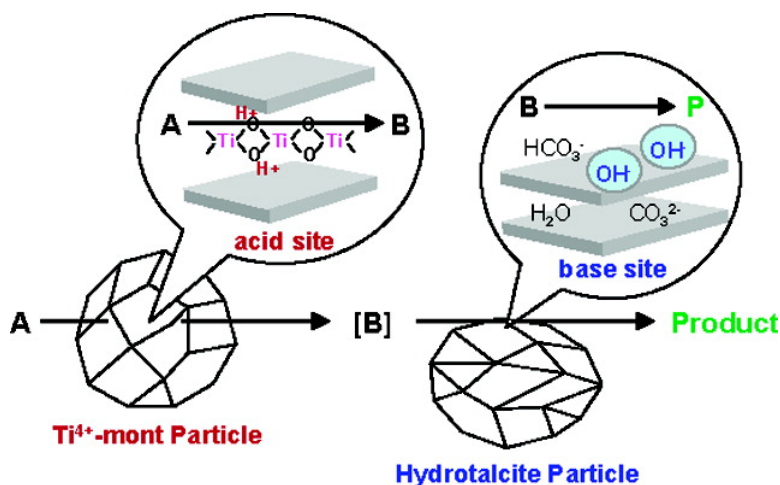
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An Acidic Layered Clay Is Combined with A Basic Layered Clay for One-Pot Sequential Reactions

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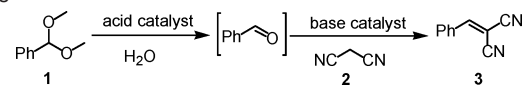Received April 12, 2005; E-mail: kaneda@cheng.es.osaka-u.ac.jp

Multireaction in a single reactor is considered desirable as a chemical process because of being operationally simple.[1,2] A significant problem in one-pot synthesis is the mutual destruction of reagents. To overcome this problem, several attractive methods, for example, anchoring active sites onto polymers[3a,b] and doping of reactive species into sol−gel materials,[3c−e] have been developed. However, at present, such solid reagents still suffer from deactivation by interaction between opposing anchored reagents and require expensive dopants as active sites as well as tedious preparation methods.

As an alternative, our strategy for the design of heterogeneous catalysts focuses on the utilization of layered clays, which can generate strong acid or base sites for catalytic functionality.[4] The Ti^{4+}-exchanged montmorillonite (Ti^{4+}-mont) is an excellent solid Brønsted acid catalyst as a result of Ti^{4+} cations in the interlayer spaces.[4a−e,5] In contrast, the surface tunable basicity of hydrotalcites (HTs) plays a crucial role in nanoscale designs of promising solid base catalysts.[4f,g,6] Since the large HT particles cannot enter the narrow interlayer of the Ti^{4+}-mont, these catalysts have the potential to be combined, allowing both acid and base sites to act independently as catalytically active centers without mutual destruction even in a same reactor. In this contribution, we present novel acid−base catalyses consisting of the Ti^{4+}-mont and HTs for unprecedented one-pot reaction sequences.

The Ti^{4+}-mont was prepared by treatment of Na^+-mont (Kunipia F, Kunimine Industry Co. Ltd.; Na, 2.69; Al, 11.8; Fe, 1.46; Mg, 1.97%) with an aqueous solution of $TiCl_4$ and was characterized by XRD, XPS, elemental analysis, and Ti K-edge XAFS.[4a] The formation of a chainlike titanium species within the mont interlayers was observed. A Mg−Al hydrotalcite (HT), $Mg_6Al_2(OH)_{16}CO_3$, was obtained from TOMITA Pharmaceutical Co., Ltd. A hydrotalcite-supported palladium nanoparticle (Pd/HT) was prepared from reaction of the HT with K_2PdCl_4 by the impregnation method followed by reduction using molecular hydrogen. EDX and TEM analyses showed the formation of Pd nanoclusters on the HT surface.

Deacetalization is an important acid-catalyzed reaction in organic synthesis, forming carbonyl compounds that are often further reacted to the target products using base catalysts. One-pot synthesis of benzylidene malononitrile (**3**) from malononitrile (**2**) with benzaldehyde dimethylacetal (**1**) was demonstrated using various acid−base catalyst pairs (Table 1). Remarkably, reaction of **1** with **2** directly proceeded in the presence of both the Ti^{4+}-mont catalyst and the HT catalyst to afford **3** in 93% yield (entry 1).[7] In the absence of the HT catalyst, benzaldehyde became the only product (entry 2), while no reaction occurred without the Ti^{4+}-mont (entry 3). From these results, **3** was considered to form via the Ti^{4+}-mont-catalyzed deacetalization of **1**,[4d] followed by the aldol reaction of **2** with benzaldehyde at the base sites of the HT.[4g] When either the Ti^{4+}-mont or the HT was replaced by a homogeneous reagent, such as *p*-toluenesulfonic acid or piperidine, both the deacetalization and aldol reactions scarcely occurred (entries 4, 5). *Furthermore, this*
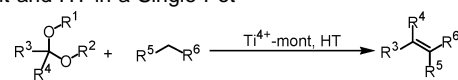
Table 1. Tandem Deprotection−Aldol Reaction with Acids and Bases[a]

entry	acid	base	conversion of **1** (%)[b]	yield of **3** (%)[b]
1	Ti^{4+}-mont	HT	>99	93
2	Ti^{4+}-mont		30	trace
3		HT	trace	trace
4[c]	Ti^{4+}-mont	piperidine	10	trace
5[d]	*p*-TsOH·H_2O	HT	trace	trace

[a] **1** (1 mmol), **2** (1 mmol), Ti^{4+}-mont (0.02 g; Ti: 0.013 mmol), HT (0.15 g), toluene (3 mL), 1 h, 80 °C. [b] Determined by GC. [c] Piperidine (0.15 mmol). [d] *p*-Toluenesulfonic acid (0.1 mmol).

Table 2. Tandem Deprotection−Aldol Reaction Using the Ti^{4+}-mont and HT in a Single Pot[a]

| | acetal | | | | donor | | time | isolated |
entry	R^1	R^2	R^3	R^4	R^5	R^6	(h)	yield (%)
1	Me	Me	Ph	H	CN	CN	1	90
2[b]	$-C_2H_2-$		Ph	H	CN	CN	1	88
3[b]	$-C_2H_2-$		3-TMS−Ph	H	CN	CN	1	82
4	Me	Me	Ph	H	CN	COOMe	1	95
5[c]	Me	Me	Ph	H	CN	PhC(O)	12	83
6[d]	Me	Me	PhC_2H_2	H	CN	COOMe	1	79
7[e]	Me	Me	n-C_5H_{11}	H	CN	Ph	2.5	81[f]
8[b]	$-C_2H_2-$		$-C_5H_{10}-$		CN	CN	10	68

[a] Acetal (1 mmol), donor (1 mmol), Ti^{4+}-mont (0.02 g; Ti: 0.013 mmol), HT (0.2 g), toluene (3 mL), 80 °C. [b] 1,4-Dioxane was used as solvent. [c] At 100 °C. [d] At 60 °C, (*E*)-acetal was used. [e] At 150 °C. [f] *E/Z* = 1/11.

*one-pot reaction system did not need the addition of water (entry 1) because the successive aldol reaction produced water to efficiently accelerate the deprotection of **1**.*[8] Deacetalizations have often been performed in aqueous organic solvents despite tedious separating procedures.[9] The present tandem catalytic reaction system can contribute considerably to the creation of simple and "green" industrial processes.

The scope of the one-pot deprotection−aldol reaction of acetals with equimolar amounts of donors is shown in Table 2.[10,11] The reaction of **1** with methyl cyanoacetate proceeded quantitatively to afford benzylidene methylcyanoacetate (entry 4), and ethylene ketal also gave the corresponding unsaturated nitrile in a high yield (entry 8). 2-(3′-(Trimethylsilyl)phenyl)-1,3-dioxolane reacted smoothly without decomposition of the TMS group (entry 3), in contrast to some acid catalysts which promote hydrolysis of the TMS during the deprotection process.[12] Base-promoted cross aldol reaction of aldehydes having α-protons of carbonyl groups often lead to undesirable side reactions. Using our combined catalyst system, the reaction of hexanal dimethylacetal with phenylacetonitrile gave 2-phenyl-2-octenenitrile in 92% GC yield, in which the formation of a self-aldol product was depressed because of the low concentra-

Table 3. Tandem Michael Reaction−Protection Using the HT and Ti^{4+}-mont in a Single Pot^a

entry	acceptor	donor	conditions of Michael reaction	product	Isolated yield (%)
1	**4a**	**5a**	40 °C, 2 h	**6a**	89
2	**4a**	**5b**	40 °C, 3 h	**6b**	89
3	**4b**	**5a**	50 °C, 3 h	**6c**	86
4	**4c**	**5a**	50 °C, 3 h	**6d**	70
5^{b,c}	**4c**	**5c**	100 °C, 10 h	**6e**	82
6^{c,d}	**4d**	**5d**	40 °C, 3 h	**6f**	64

^{a} Acceptor (1 mmol), donor (2 mL), Ti^{4+}-mont (0.15 g), HT (0.1 g). After the completion of Michael reaction, ethane-1,2-diol (1.5 mmol) and toluene (10 mL) were added followed by acetalization under Dean−Stark conditions for 1 h. ^{b} Donor (1.2 mmol) was used. ^{c} Toluene (2 mL) was used as solvent for Michael reaction. ^{d} Donor (1 mmol) and ethane-1,2-diol (1.1 mmol) were used.

Scheme 1
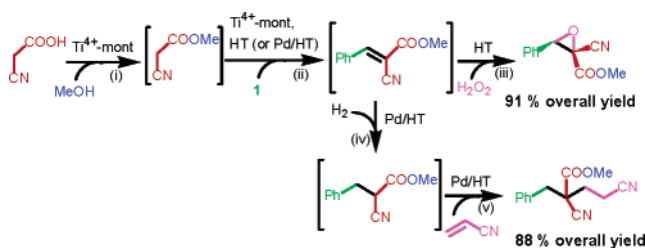
tion of the aldehyde during this one-pot reaction (entry 7). On the contrary, the use of *n*-hexanal itself in place of hexanal dimethylacetal resulted in the desired product in 71% GC yield together with 2-butyl-2-octenal. The solid mixture consisting of the Ti^{4+}-mont and HT catalysts was easily recovered by simple filtration and then could be reused at least five times with retention of high catalytic activity and selectivity.[13] *Clearly, mutual neutralization of the acid and base catalysts can be avoided using this system in a single reactor.*

The present catalyst system is also applicable to tandem Michael reaction[4g] and acetalization,[4b] as summarized in Table 3. These reactions gave excellent yields of nitrodioxolanes (entries 1−4), which are highly useful precursors for several nitro-group transfer reactions.[14] For example, nitromethane underwent the Michael reaction with methyl vinyl ketone, followed by acetalization with ethane-1,2-diol to afford an 89% yield of 2-methyl-2-(3-nitropropyl)-1,3-dioxolane (entry 1), whereas the conventional two-step method gave less than 70% yield.[14b] Also, the tandem reaction of dimethyl malonate with 2-cyclohexene-1-one readily proceeded (entry 5), and in the case of a β-ketoester, chemoselective acetalization toward an aldehyde function occurred to give a protected Michael adduct (entry 6).

The potential benefits of using these clay catalysts together are highlighted by the development of novel one-pot synthetic processes (Scheme 1). Epoxynitrile, an intermediate for the synthesis of various heterocyclic compounds,[15] was successfully obtained using methanol, cyanoacetic acid, **1**, and hydrogen peroxide in four sequential acid and base reactions, namely, esterification (i),[4e] deacetalization (ii), aldol reaction (ii), and epoxidation (iii),[4f] in a single reactor. We also succeeded in a one-pot synthesis of glutaronitrile using the Ti^{4+}-mont and Pd/HT catalysts. After reduction of the unsaturated nitrile under 1 atm of H$_2$ (iv), Michael reaction with

acrylonitrile occurred at the base sites of the Pd/HT to afford 2-carbomethoxy-2-benzyl glutaronitrile in an excellent overall yield (v).[16] *To the best of our knowledge, these are the first demonstrations of one-pot synthesis consisting of more than four catalytic acid and base reactions.*

In conclusion, isolated catalytically active centers could be created based on clay materials for realization of a variety of acid−base tandem reactions. This protocol has several advantages: (I) the ease of preparing the solid catalysts, (II) high catalytic activities, (III) wide applicability to several acid or base reactions, (IV) simple workup procedure, and (V) reusability. Our concept can be applied to other various one-pot incompatible systems and make a contribution toward the creation of environmentally inspired chemical processes through the promotion of multiple reactions in a single reactor.

References

(1) Hall, N. *Science* **1994**, *266*, 32.
(2) For excellent reports of one-pot reactions, see: (a) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465. (b) Kawasaki, T.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 5138. (c) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101. (d) Choudary, B. M.; Chowdari, N. S.; Madhi, S.; Kantam, M. L. *J. Org. Chem.* **2003**, *68*, 1736. (e) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551.
(3) (a) Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1977**, *99*, 4165. (b) Cainelli, G.; Contento, M.; Manescalchi, F.; Regnoly, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2516. (c) Gelman, F.; Blum, J.; Avnir, D. *J. Am. Chem. Soc.* **2000**, *122*, 11999. (d) Gelman, F.; Blum, J.; Avnir, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3647. (e) Gelman, F.; Blum, J.; Avnir, D. *J. Am. Chem. Soc.* **2002**, *124*, 14460.
(4) For acidic clays: (a) Ebitani, K.; Kawabata, T.; Nagashima, K.; Mizugaki, T.; Kaneda, K. *Green Chem.* **2000**, *2*, 157. (b) Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2001**, *42*, 8329. (c) Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2003**, *125*, 10486. (d) Kawabata, T.; Kato, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Lett.* **2003**, *32*, 648. (e) Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2003**, *44*, 9205. For basic clays: (f) Yamaguchi, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* **2000**, *65*, 6897. (g) Motokura, K.; Nishimura, D.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 5662.
(5) For mont-catalyzed organic synthesis, see: (a) Pinnavaia, T. J. *Science* **1983**, *220*, 365. (b) Laszlo, P. *Acc. Chem. Res.* **1986**, *19*, 121. (c) Izumi, Y.; Onaka, M. *Adv. Catal.* **1992**, *38*, 245.
(6) For HT catalysts, see: (a) Sels, B. F.; De Vos, D. E.; Buntinx, M.; Pierard, F.; Kirsch-De Mesmaeker, A.; Jacobs, P. A. *Nature* **1999**, *400*, 855. (b) Sels, B. F.; De Vos, D. E.; Jacobs, P. A. *Catal. Rev.* **2001**, *43*, 443. (c) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127. (d) Palomares, A. E.; Prato, J. G.; Rey, F.; Corma, A. *J. Catal.* **2004**, *221*, 62.
(7) The Ti^{4+}-mont and HT catalysts showed higher activities than those of other solid acid (see ref 4b) and base catalysts (see Supporting Information), such as zeolites and MgO.
(8) The first path of the deacetalization proceeded using water adsorbed on the Ti^{4+}-mont.
(9) (a) Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 1027. (b) Dalpozzo, R.; De Niro, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A.; Sindona, G.; Bartoli, G. *J. Org. Chem.* **2002**, *67*, 9093.
(10) The reaction of simple alkynlnitriles with high pK_a values (~31) did not occur under the present conditions.
(11) The estimated turnover numbers of acid and base sites were calculated to be 25 and 7, respectively; see Supporting Information.
(12) Yamakawa, T.; Kagechika, H.; Kawachi, E.; Hashimoto, Y.; Shudo, K. *J. Med. Chem.* **1990**, *33*, 1430.
(13) In the reaction of methyl cyanoacetate with **1**, the yields of the first, second, and fifth runs were 95, 95, and 90%, respectively.
(14) (a) Laronze, J. Y.; Laronze, J.; Patigny, D.; Levy, J. *Tetrahedron Lett.* **1986**, *27*, 489. (b) Ulrich, W.-R.; Scheufler, C.; Fuchss, T.; Senn-Bilfinger, J. Eur. Pat. Appl. 0151486, Jul 19, 2001.
(15) (a) Ammadi, F.; Boukhris, S.; Souizi, A.; Coudert, G. *Tetrahedron Lett.* **1999**, *40*, 6517. (b) Gaz, A.; Souizi, A.; Coudert, G. *Synth. Commun.* **1999**, *29*, 3459.
(16) The Pd/HT has both surface basicity and hydrogenation ability. For details of the bifunctional catalysis of the Pd/HT, see: Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.*, in press.

JA052386P