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Highly Efficient C−C Bond-Forming Reactions in Aqueous Media Catalyzed by Monomeric Vanadate Species in an Apatite Framework

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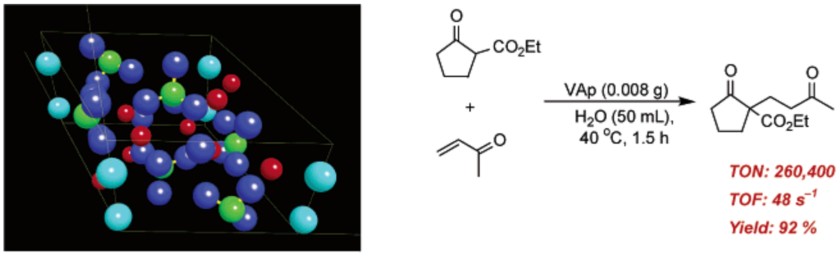
Received July 16, 2006



A calcium vanadate apatite (VAp), in which PO_4^{3-} of hydroxyapatite (HAP), $Ca_{10}(PO_4)_6(OH)_2$, is completely substituted by VO_4^{3-} in the apatite framework, was synthesized. Physicochemical analysis of the VAp reveals the presence of isolated VO_4 tetrahedron units with a pentavalent oxidation state. The VAp acts as a high-performance heterogeneous base catalyst for various carbon−carbon bond-forming reactions such as Michael and aldol reactions in aqueous media and the H−D exchange reactions using deuterium oxide. For example, a 200-mmol-scale Michael reaction under triphasic conditions proceeded rapidly, with an extremely high turnover number of up to 260 400 and an excellent turnover frequency of 48 s^{-1}. No vanadium leaching was detected during the above reactions, and the catalyst was readily recycled with no loss of activity.

Introduction

Vanadium is one of the most essential metals in catalysis due to its versatile redox potential, unique oxygen-transfer ability, and highly Lewis acidic properties.[1] These characteristics have facilitated the development of a diverse array of oxidative transformations that cannot be achieved using other transition metal catalysts,[2] but the use of vanadium catalysts in carbon−carbon bond-forming reactions has lagged far behind.[3] The ability to precisely control the architecture of active vanadium centers is expected to lead to the discovery of new synthetic methods involving fascinating and atom-economical carbon−carbon bond formations.

The use of water as a reaction medium instead of organic solvents is another approach to elucidating novel synthetic methodologies. Reports on aqueous reactions have become increasingly frequent and specialized over the past few years.[4] Unique reactivity and selectivity that cannot be achieved under dry conditions are often observed in aqueous reactions due to

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(1) (a) Crans, D. C.; Smee, J. J. In *Comprehensive Coordination Chemistry II*; McCleverty, J. A., Meyer, T. J., Ed.; Pergamon: London, 2004; Vol. 4, pp 175−239. (b) Bolm, C. *Coord. Chem. Rev.* **2003**, *237*, 245. (c) Misono, M. *Top. Catal.* **2002**, *21*, 89. (d) Gao, X.; Wachs, I. E. *Top. Catal.* **2002**, *18*, 243. (e) Hirao, T. *Chem. Rev.* **1997**, *97*, 2707.

(2) The regio- and stereoselective epoxidation of allylic alcohols using oxovanadium compounds in combination with *tert*-butyl hydroperoxide have been especially studied in detail. For example: (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (b) Ito, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.

(3) Recent notable reports for oxovanadium-catalyzed carbon−carbon bond formations. See: (a) Trost, B. M.; Jonasson, C.; Wuchrer, M. *J. Am. Chem. Soc.* **2001**, *123*, 12736. (b) Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230.

(4) Advantages of organic syntheses under aqueous conditions have been highlighted in the following literatures. See: (a) Li, C.-J., Chan, T.-H., Eds.; *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (c) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2002**, *8*, 4095.

10.1021/jo0614745 CCC: $33.50

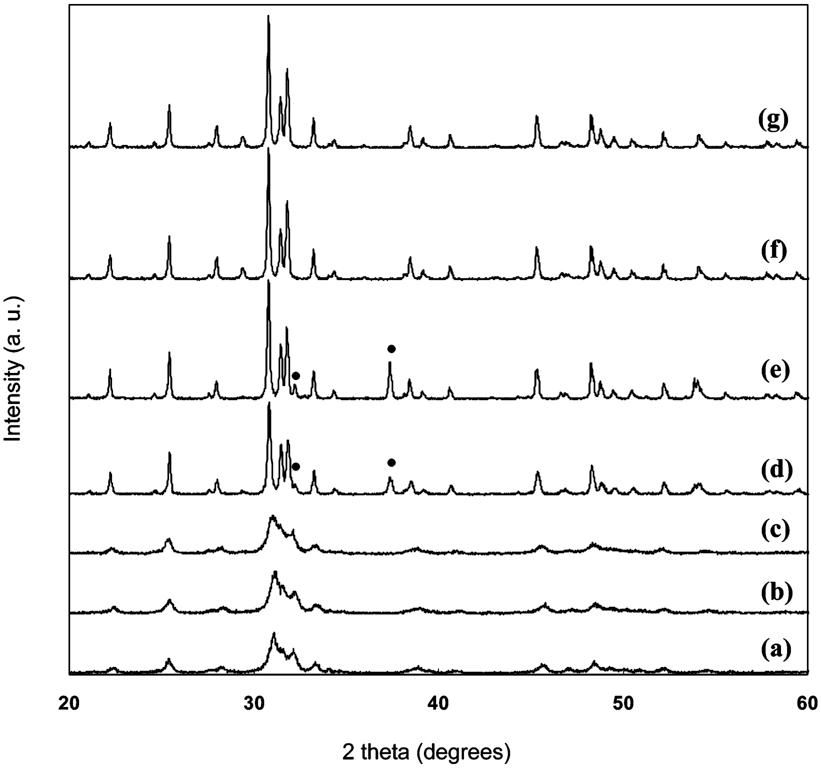

FIGURE 1. Variation of XRD patterns upon the calcination temperature for VAp: (a) uncalcined, (b) 200 °C, (c) 400 °C, (d) 600 °C, (e) 800 °C, (f) recovered VAp after the aqueous Michael reaction of **1a** with **2a**, and (g) treatment with water by Soxhlet's extractor after calcination at 800 °C. The peaks labeled (●) are originated from CaO.

the hydrophilic and hydrogen-bonding properties of water, even when solid catalysts are employed. Conducting reactions under aqueous conditions also provides the advantages such as reduced pollution, low cost, and simplicity in process and handling. These factors are especially important in an industry aiming at Green & Sustainable Chemistry.

Apatites and related compounds are of great interest because of their structural stability and their potential for cationic and anionic isomorphous substitution.[5] The hexagonal hydroxyapatite (HAP) structure comprises Ca^{2+} sites surrounded by PO_4^{3-} tetrahedra. The chemical composition of HAP can be modified from the stoichiometric form, $Ca_{10}(PO_4)_6(OH)_2$ (Ca/P = 1.67), to the nonstoichiometric Ca-deficient form, $Ca_{10-Z}(HPO_4)_Z(PO_4)_{6-Z}(OH)_{2-Z}$ ($0 < Z \leq 1$, $1.5 \leq$ Ca/P < 1.67). We have previously focused on doping the apatite surface with various transition metal cations, which can function as catalytically active centers, via cation exchange at Ca^{2+} sites.[6] For example, the introduction of La^{3+} cation into the apatite can generate stable monomeric phosphate complexes, which act as efficient heterogeneous catalysts for the Michael reaction of 1,3-dicarbonyls with enones under aqueous or solvent-free conditions.[6b,6c]

Here, we present a new strategy for the design of a nanoconstructed heterogeneous catalyst and the synthesis of a calcium vanadate apatite (VAp), $Ca_{10}(VO_4)_6(OH)_2$, by substituting VO_4^{3-} for PO_4^{3-} in the whole apatite matrix. With water as a reaction medium, the VAp exhibited exceptionally high catalytic activities for carbon−carbon bond-forming reactions. Our catalytic system possesses remarkably attractive features for organic synthesis: (i) high catalytic efficiency under mild reaction conditions, (ii) a simple procedure which allows for large-scale operation, (iii) no requirement for organic solvents, and (iv) easy separation and recycling of the solid catalyst. To the best of our knowledge, *this is the first report of* successful carbon−carbon bond-forming reactions under aqueous conditions using vanadium as a Brønsted base catalyst.

Results and Discussion

Catalyst Preparation and Characterization. The VAp was synthesized by modification of a previously reported procedure.[7] A mixture of $CaSO_4 \cdot 2H_2O$ and Na_3VO_4 in aqueous solution was refluxed for 2 h with excess NaOH. The resulting white slurry was cooled to room temperature, filtered, washed with deionized water and dried, followed by calcination in air at 800 °C for 3 h, yielding the VAp as a white powder. Based on elemental analysis, the amounts of Ca and V were found to be 35.03 and 26.58 wt %, respectively, and the Ca/V ratio of the VAp was 1.67 in agreement with the stoichiometric value of the apatite components. The Brunauer−Emmett−Teller (BET) surface area was found to be 1.1 $m^2 \cdot g^{-1}$. The powder X-ray diffraction (XRD) patterns of the VAp calcined at various temperatures are shown in Figure 1. The intensities of the

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(5) Elliott, J. C. *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates*; Elsevier: Amsterdam, 1994.

(6) (a) Mori, K.; Mitani, Y.; Hara, T.; Mizugaki, T. Ebitani, K.; Kaneda, K. *Chem. Commun.* **2005**, 3331. (b) Mori, K.; Oshiba, M.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2005**, *46*, 4283. (c) Mori, K.; Oshiba, M.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *New. J. Chem.* **2006**, *30*, 44. (d) Mori, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc*. **2004**, *126*, 10657. (e) Mori, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc*. **2003**, *125*, 11460. (f) Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572. (g) Yamaguchi, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc*. **2000**, *122*, 7144.

(7) Mayer, I.; Wahnon, S.; Cohen, S. *Mater. Res. Bull.* **1979**, *14*, 1479.

diffraction peaks of VAp lattice increased with increasing calcination temperatures: the uncalcined VAp showed an amorphous phase, whereas the VAp samples calcined at more than 600 °C exhibited sharp peaks together with small peaks of a CaO phase at around 32° and 38°.

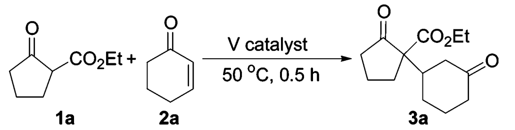
Transmission electron microscopy (TEM) images of the VAp calcined at 800 °C show that the VAp covered with amorphous CaO phase was observed as a bright region in a dark field.[8] The Ca/V ratio at various depths of the VAp matrix was determined by XPS etched by Ar ion laser. First, enrichment of Ca at the surface was observed due to the presence of the CaO phase. As the etch treatment was continuously repeated, the Ca/V ratio decreased, but then increased again. It seems that the VAp consists of three phases: CaO, a nonstoichiometric VAp shell, e.g. $Ca_9(HVO_4)(VO_4)_5(OH)$,[9] and a stoichiometric VAp core from the surface.[5] Allowing other characterization results confirmed by several physicochemical methods,[8] *the present methodology of catalyst preparation is a promising protocol for creation of a nonstoichiometric apatite phase containing stable and isolated tetrahedral vanadium species with an oxidation state of +5 on an apatite surface.*

VAp-Catalyzed Aqueous Michael Reaction. The Michael reaction of 1,3-dicarbonyl compounds with activated enones provides access to 1,5-dioxo synthons, which can be easily transformed into cyclohexanone derivatives for use as important intermediates in steroid and terpenoid synthesis.[10] Traditionally, this reaction is promoted by strong bases such as alkali metal alkoxides or hydroxides.[11] In some cases, however, a number of side- and subsequent reactions, e.g. ester solvolysis, aldol-cyclizations, and retro-Claisen-type decompositions result in low selectivity. One way to address these drawbacks is to avoid Brønsted basic reaction conditions. To achieve this, a number of catalytic systems employing neutral conditions have been developed.[12]

To investigate the abilities of the VAp catalyst, the Michael reaction of 2-oxo-cyclopentane carboxylic acid ethyl ester (**1a**) with 2-cyclohexen-1-one (**2a**) was carried out as a model reaction at 50 °C in various solvents. The results are summarized in Table 1.

It is noteworthy that the VAp showed high catalytic activity for the Michael reaction under aqueous conditions, giving only 2-oxo-1-(3-oxocyclohexyl)-cyclopentane carboxylic acid ethyl ester (**3a**) in a quantitative yield within 30 min (entry 1). The reaction did not proceed at all without the VAp catalyst (entry 27), and no product was formed when any other polar or nonpolar solvent was used (entries 6−16). Comparisons of the catalytic activities of the VAp with those of various vanadium compounds in a water solvent are also summarized in Table 1.

TABLE 1. Michael Reaction of 1a with 2a[a]



entry	catalyst[b]	solvent	convn (%)[c]	yield (%)[c]
1	VAp (800 °C)	water	>99	>99
2	VAp (600 °C)	water	20	18
3	VAp (400 °C)	water	11	10
4	VAp (200 °C)	water	2	2
5[d]	VAp (uncalcined)	water	38	36
6	VAp (800 °C)	neat	0	0
7	VAp (800 °C)	acetone	0	0
8	VAp (800 °C)	CH_3CN	0	0
9	VAp (800 °C)	EtOH	0	0
10	VAp (800 °C)	EtOAc	0	0
11	VAp (800 °C)	DMF	0	0
12	VAp (800 °C)	DMSO	0	0
13	VAp (800 °C)	1,4-dioxane	0	0
14	VAp (800 °C)	CH_3NO_2	0	0
15	VAp (800 °C)	THF	0	0
16	VAp (800 °C)	toluene	0	0
17	Na_3VO_4	water	41	39
18	K_3VO_4	water	33	32
19	$Mg_2V_2O_7$	water	19	17
20	$NaVO_3$	water	0	0
21	$VO(acac)_2$	water	0	0
22	$V(acac)_3$	water	0	0
23	V_2O_5	water	0	0
24	$VOSO_4 \cdot nH_2O$	water	0	0
25	VCl_3	water	0	0
26	HAP	water	0	0
27	none	water	0	0

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), catalyst (V: 0.012 mmol), solvent (3 mL). [b] Values in parentheses are calcination temperature. [c] Determined by GC using an internal standard technique. [d] Vanadium leaching was observed.

It appears that the calcination process of the VAp is indispensable in the formation of the active VAp catalyst; as the temperature of calcination increases to 800 °C, the catalytic activity of the resulting VAp increases (Table 1, entries 1−5). This result supports the finding of the XRD analysis, in which the peak intensities of the resulting VAp lattice increase as the calcination temperature is raised (Figure 1a−e). Orthovanadate and pyrovanadate derivatives containing isolated VO_4 tetrahedra, such as Na_3VO_4, K_3VO_4, and $Mg_2V_2O_7$ also gave **3a** in moderate yields of 39%, 32%, and 17%, respectively (entries 17−19), but these catalysts underwent severe deactivation caused by the structural change from monomeric to polymerized species during the reaction: the presence of charge-transfer bands at wavelengths longer than 320 nm was confirmed by UV−vis spectroscopy. The use of other vanadium reagents did not afford any products (entries 20−25), and the reaction did not proceed in the presence of the HAP by itself (entry 26). These results support the contention that the presence of isolated VO_4 tetrahedral species on a solid surface plays a key role in the success of the aqueous Michael reaction.

The VAp-catalyzed Michael reaction in water was found to be expandable to include various sets of donors and acceptors. The results are summarized in Table 2. It was found that the aqueous Michael reaction of **1a** with 3-buten-2-one (**2b**) proceeded efficiently in the presence of the VAp catalyst to give 2-oxo-1-(3-oxobutyl)-cyclopentanecarboxylic acid ethyl ester (**3b**) quantitatively in 10 min (entry 1). Methyl acrylate (**2c**) and acrylonitrile (**2d**) also acted as good acceptors, giving

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(8) See Supporting Information.

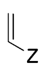
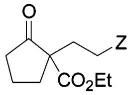
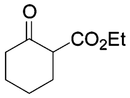
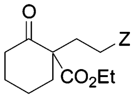
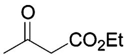
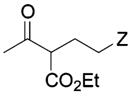
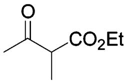
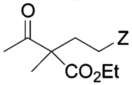
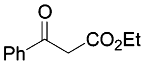
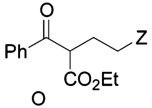
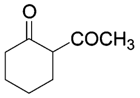
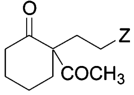
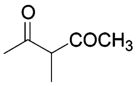
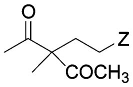
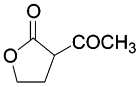
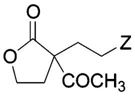
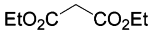
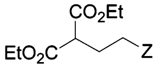
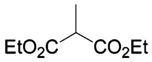
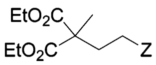
(9) The crystallographic structure of the Ca-deficient HAp is identical to that of the stoichiometric one, and its charge deficiency due to the lack of Ca^{2+} in the lattice is compensated by introduction of H^+ into the PO_4^{3-} ion and removal of OH^- in the parent unit cell.

(10) (a) Ho, T.-L. *Tactics of Organic Synthesis*; Wiley: New York, 1994. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon: Oxford, 1991; Vol. 4; pp 1. (c) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; p 595.

(11) (a) Perlmutter, P. *Cojugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series, Vol. 9; Pergamon: Oxford, 1992. (b) Oare, D. A.; Heathcock, C. H. *Top. Stereochem*. **1989**, *19*, 227. (c) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React*. **1959**, *10*, 179.

(12) Pelzer, S.; Kauf, T.; van Wüllen, C.; Christoffers, J. *J. Organomet. Chem*. **2003**, *684*, 308. For an excellent review on transition metal catalyzed Michael reaction of 1,3-dicarbonyls, see: (b) Christoffers, J. *Eur. J. Org. Chem*. **1998**, *1259*, 9.

TABLE 2. Aqueous Michael Reaction in the Presence of VAp Catalyst[a]

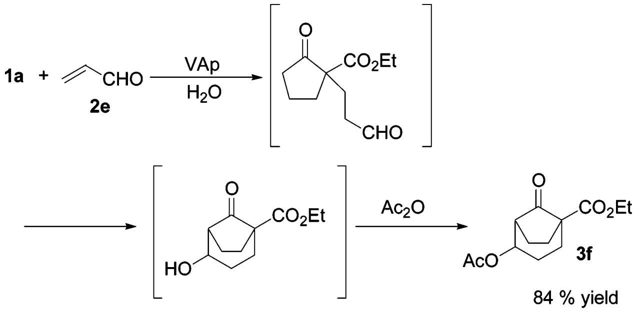
entry	donor	acceptor	time (h)	product	yield (%)[b]
1[c]	**1a**	 **2b** Z=COCH$_3$	10 min.	 **3b**	>99 (96)
2[d]	**1a**	**2c** Z=CO$_2$Me	3	**3c**	92
3[d]	**1a**	**2d** Z=CN	3	**3d**	93
4		**2b**	1		98
5	 **1b**	**2b**	1.5	 **3e**	93
6		**2b**	2		>99
7		**2b**	2		98 (90)
8		**2b**	1		>99
9		**2b**	1		>99
10		**2b**	2		94
11[d]		**2c**	2		98
12[d]		**2d**	2		96
13[e]	 **1c**	**2b**	1		94 (92)
14[f]	 **1d**	**2b**	3		98

[a] Donor (5 mmol), acceptor (5.5 mmol), VAp (0.05 g), H_2O (5 mL), 30 °C. [b] Determined by GC using an internal standard technique. Values in parentheses are isolated yield. [c] VAp (0.025 g). [d] 50 °C. [e] **2b** (20 mmol), without solvent, 80 °C. [f] **2b** (10 mmol), without solvent, 80 °C.

3c and **3d**, respectively (entries 2 and 3). The reaction of **2b** with various β-keto esters, 1,3-diketones, and lactone with **2b** afforded high yields of the corresponding 1,5-dioxo compounds (entries 4−12). The Michael reactions of diethylmalonate derivatives (**1c** and **1d**) with **2b**, which did not easily proceed by use of traditionally Lewis acid catalysts, gave the corresponding products in excellent yields (entries 13 and 14).

In all cases, the 1,4-addition products were obtained exclusively without formation of 1,2-adducts. Unfortunately, the use of 2-acetylpentanone, acetylacetone, and ethyl benzoyl acetate, which have low pK_a values of 7.8, 9.0, and 9.4[13] as donors was not effective in the present Michael reaction, and it resulted in the dissolution of vanadium into the reaction mixture. This leaching of vanadium may be the result of strong coordination by the donors to the surface vanadium species, thus preventing smooth reactions.[14] In the reaction of **1a** with acrolein (**2e**), sequential intramolecular 1,2-addition reaction and acetylation proceeded to give 4-acetoxy-8-oxobicyclo[3.2.1]-octan-1-carboxylic acid ethyl ester (**3f**) (Scheme 1).[15]

SCHEME 1



84 % yield

The workup procedure is straightforward due to the heterogeneous nature of the catalyst and the three-phase reaction mixture, as shown in Figure 2.

The product was easily separated by extraction after filtering out the solid catalyst. No spectral change was observed in the UV−vis or XAFS spectra of the recovered VAp, which shows that the vanadium species remained in the monomeric state throughout the reaction. The catalyst was found to be reusable at least four times without any reduction in activity during the reaction of **1a** and **2b**.[8] To further demonstrate the effectiveness of the VAp, the catalyst was removed by filtration from the reaction of **1b** with **2b** after 55% conversion. Continuation of the reaction for 1 h under identical reaction conditions afforded no product (Figure 3). Any vanadium leached in the aqueous

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(14) Selbin, J.; Maus, G.; Johnson, D. L. *J. Inorg. Nucl. Chem.* **1967**, *29*, 1735.

(15) (a) Buchanan, G. L.; McLay, G. W. *Tetrahedron* **1966**, *22*, 1521. (b) Kraus, W.; Patzelt, H.; Sadlo, H.; Sawitzki, G.; Schwinger, G. *Liebigs Ann. Chem.* **1981**, 1826.

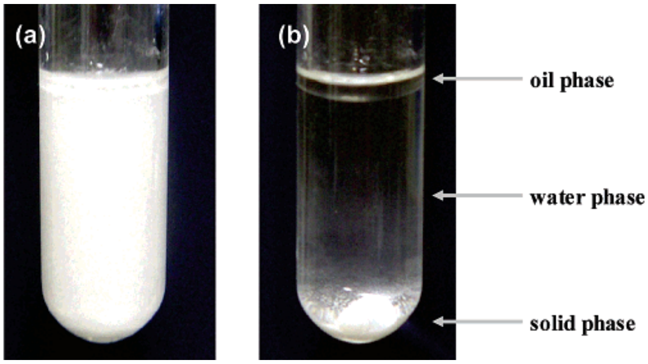


FIGURE 2. Aqueous Michael reaction of **1b** with **2b**: (a) reaction mixture and (b) three-phase separation by a centrifuge after the reaction.

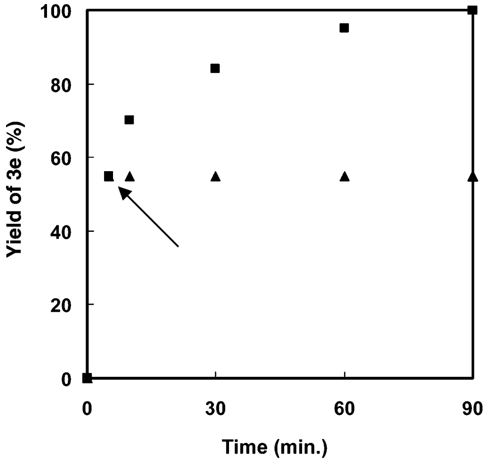
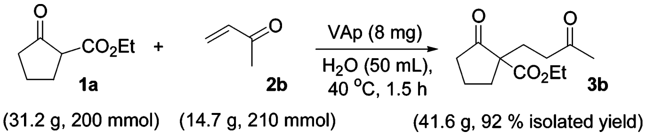


FIGURE 3. Effect of removal of the VAp catalyst on the Michael reaction of **1c** with **2b**: without removal of VAp (■); an arrow indicates the removal of the VAp (▲). Reaction conditions: **1c** (5 mmol), **2b** (5.5 mmol), VAp (0.05 g), water (5 mL), 30 °C.

SCHEME 2



phase was in amount small enough to be undetectable by ICP analysis. These results show that *this reaction proceeds on the VAp surface and does not involve dissolved vanadium species.*

More significantly, the use of 8 mg of the VAp catalyst under aqueous conditions allowed 32.2 g (200 mmol) of **1a** to react with 15.4 g (210 mmol) of **2b** in a highly effective manner, giving a 92% isolated yield (41.6 g) of **3b** at 40 °C in 1.5 h, as highlighted in Scheme 2. It has been reported that the surface density of PO_4^{3-} species of the HAP is 5 PO_4^{3-} nm^{-2}.[16] Adapting this calculation method, the amount of the VO_4^{3-} in the spent VAp was estimated to be 0.096 $mmol \cdot g^{-1}$ for the surface area. Based on the surface vanadium content, the VAp catalyst showed a high turnover number (TON; mol of product per mol of surface V content) of 260 400 and turnover frequency (TOF; mol of product per mol of surface V content per second) of 48 s^{-1}. In contrast, our previously reported aqueous Michael reactions using hydroxyapatite-supported La complex (LaHAP) catalyst,[6b,6c] montmorillonite-enwrapped Sc (Sc^{3+}-mont),[17a] and montmorillonite-enwrapped Cu (Cu^{2+}-mont)[17b] gave TONs of 4500, 1000, and 400 and TOFs of 500, 29, and 28.5 h^{-1}, respectively. The TON and TOF values of the VAp catalyst are the highest ever reported for the transition metal catalyzed Michael reactions so far: $RuH_2(PPh_3)_4$ (TON 33.3, TOF 66.6 h^{-1}),[18] $Yb(OTf)_3/SiO_2$ (17, 0.7 h^{-1}),[19] $CeCl_3 \cdot 7H_2O/NaI$ (5, 0.8 h^{-1}),[20] $Ni(acac)_2$ (100, 100 h^{-1}),[21] Fe-mica (100, 5 h^{-1}),[22] $InCl_3$ (10, 1.7 h^{-1}),[23] $Yb(OTf)_3$ (100, 1.4 h^{-1})[24] and $FeCl_3 \cdot 6H_2O$ (100, 100 h^{-1}).[25] We concluded that the present vanadium-based catalytic system allows for simple and practical organic synthesis while meeting the increasing criteria for environmentally friendly chemical processes in the synthesis of fine chemicals and pharmaceuticals.

VAp-Catalyzed Aldol-Type Reaction. To explore the promising catalytic activity of the VAp in the abstraction of acidic α-hydrogenes from various carbonyl compounds, several aldol-type reactions were examined under aqueous conditions. It is well-known that Knoevenagel condensation of aldehydes with active methylene compounds is a useful tool allowing convenient carbon chain elongation along with functionalization of aldehydes, giving α,β-unsaturated carbonyls or nitriles. This reaction is usually catalyzed by bases such as amines, ammonia, or sodium ethoxide in organic solvents.[26]

Our previously reported LaHAP and Sc^{3+}-mont and catalysts, which were active for Michael reactions in water, did not promote this type of condensation. In contrast, the VAp catalyst exhibited high catalytic activity for the Knoevenagel reaction. The range of substrates for the Knoevenagel reaction under aqueous conditions is exemplified in Table 3. Preliminary screening of solvents showed that water was superior to other organic solvents for this reaction.[27] The reaction is highly stereoselective for the *E*-geometry, affording the corresponding α,β-unsaturated nitriles in excellent yields. Both electron-rich and electron-deficient benzaldehydes reacted well, giving high product yields (entries 2 and 3). Aliphatic aldehydes such as hexanal and octanal also underwent the condensation easily (entries 4 and 5). It is notable that cinnamaldehyde reacted with **4a** without formation of the 1,4-adduct (entry 7). The reaction of phenylacetonitrile (**4c**), which has a large pK_a value of 21.9,[2828] proceeded efficiently in the presence of the VAp

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[16] Tanaka, H.; Yasukawa, A.; Kandori, K.; Ishikawa, T. *Colloids Surf. A* **1997**, *125*, 53.

[17] (a) Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2003**, *125*, 10486. (b) Kawabata, T.; Kato, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Eur. J.* **2005**, *11*, 288.

[18] Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436.

[19] Kotsuki, H.; Arimura, K. *Tetrahedron Lett.* **1997**, *38*, 7583.

[20] Bartoli, G.; Bosco, M.; Bellucci, M. C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* **1999**, *617*, 7.

[21] Saegusa, T.; Ito, Y.; Tomita, S.; Kinoshita, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 496.

[22] Shimizu, K.-I.; Miyagi, M.; Kan-no, T.; Kodama, T.; Kitayama, Y. *Tetrahedron Lett.* **2003**, *44*, 7421.

[23] Yadav, J. S.; Geetha, V.; Reddy, B. V. S. *Synth. Commun.* **2002**, *32*, 3519.

[24] Keller, E.; Feringa, B. L. *Tetrahedron Lett.* **1996**, *37*, 1879.

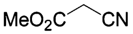
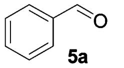
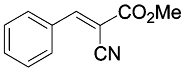
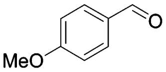
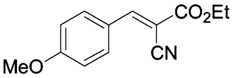
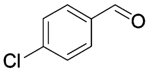
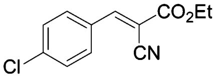
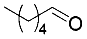
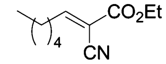
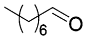
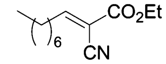
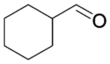
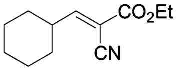
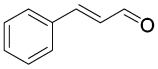
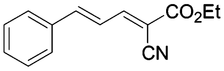
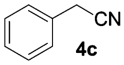
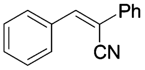
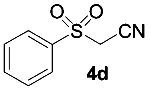
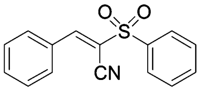
[25] Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141.

[26] (a) Marcaccini, S.; Pepino, R.; Pozo, M. C.; Basurto, S.; Garæia-Valverde, M.; Torroba, T. *Tetrahedron Lett*. **2004**, *45*, 3999. (b) Shih, M. H.; Yeh, M. Y. *Tetrahedron* **2003**, *59*, 4103. (c) Heathcock, C. H. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 341.

[27] In the screening of various solvents as summarized in Table 1, **6a** was obtained in 26% (DMSO) and 11% (EtOH), respectively. The other organic solvent resulted in no conversion of substrates.

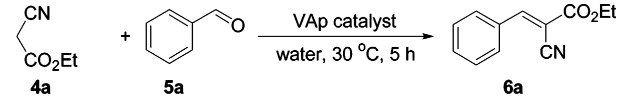
[28] Martell, A. E.; Smith, R. M. In *Critical Stability Constants*; Plenum Press: New York, 1974, 1975, 1977; Vol. 1−3.

TABLE 3. Knoevenagel Condensation in Water Using VAp Catalyst[a]

entry	donor	acceptor	time (h)	product	yield (%)[b]
1	 **4b**	 **5a**	1		>99
2	**4a**		3		98
3	**4a**		6		96
4	**4a**		4		95
5	**4a**		6		91
6	**4a**		3		99
7	**4a**		3		>99
8[c]	 **4c**	**5a**	12		89
9[d]	 **4d**	**5a**	2		90

[a] Donor (1.5 mmol), acceptor (1 mmol), water (5 mL), VAp (0.05 g), 50 °C. [b] Determined by GC using an internal standard method. [c] 110 °C. [d] THF (1 mL) was used as a cosolvent, 60 °C.

SCHEME 3



4a **5a** **6a**

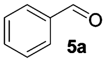
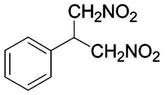
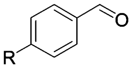
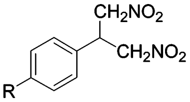
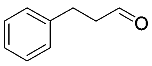
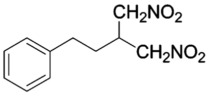
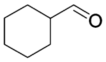
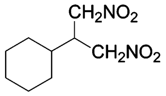
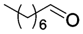
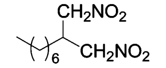
95 % isolated yield

catalyst (entry 8), but was not catalyzed efficiently by $RuH_2(PPh_3)_4$[18] as a typical metal complex, or cationic RuHAP.[6f] In the case of phenylsulfonylacetonitrile (**4d**), the condensation proceeded efficiently using THF as a cosolvent (entry 9). Other vanadium compounds of $VO(acac)_2$, $V(acac)_3$, V_2O_5, $VOSO_4 \cdot nH_2O$, and VCl_3 were also examined as potential catalysts for this reaction, but all gave inferior results or showed no conversion.[29]

Furthermore, a 100-mmol-scale condensation of ethyl cyanoacetate (**4a**, $pK_a = 9.0$) with benzaldehyde (**5a**) in water produced (2*E*)-2-cyano-3-phenyl-2-propenoic acid ethyl ester (**6a**) quantitatively (Scheme 3).

The use of nitromethane (**6**) as a donor instead of nitriles under aqueous reflux conditions afforded the corresponding 1,3-dinitro compounds predominantly, as shown in Table 4.[30] These 1,3-dinitro compounds are known to be key building blocks for biologically active substances including HIV-protease activity inhibitors and NMDA receptor antagonists.[31]

TABLE 4. Synthesis of 1,3-Dinitrocompounds Catalyzed by VAp in Water[a]

entry	acceptor		product	yield (%)[b]
1	 **5a**			91
2		R = NO2		81
3		Cl		92
4		OMe		90
5				81
6				83
7				77

[a] VAp (0.05 g), nitromethane (1 mL), acceptor (1 mmol), H_2O (5 mL), 100 °C, 12 h. [b] Isolated yield.

Electronic variation of *p*-substituted benzaldehydes did not strongly affect reaction rates. When the temperature was lowered to 30 °C in the reaction of **6** with **5a**, the corresponding nitro alcohol was obtained quantitatively. This observation suggests that the reaction may consist of three sequential reactions: aldol condensation, dehydration, and Michael reaction.[32] Furthermore,

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[29] Orthovanadate salts such as Na_3VO_4 and K_3VO_4 showed catalytic activity but resulted in poor yields.

[30] Syntheses of 1,3-dinitro compounds; see: (a) Ferro, A.; Rezende, M. C.; Sepulveda-Boza, S.; Reyes-Parada, M.; Cassels, B. K. *J. Chem. Res.* **2001**, *7*, 294. (b) Alcantara, M. D.; Escribano, F. C.; Gomez-Sanchez, A.; Dianez, M. J.; Estrada, M. B. Castro, A. L.; Perez-Garrido, S. *Synthesis* **1996**, 64.

[31] Ballini, R.; Barboni, L.; Fiorini, D.; Giarlo, G.; Palmieri, A. *Chem. Commun.* **2005**, 2633.

[32] Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. *Synthesis* **2004**, 1938.

SCHEME 4

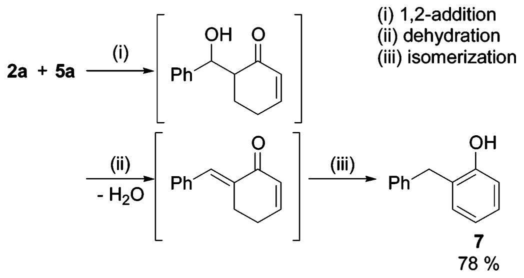
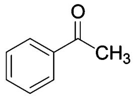
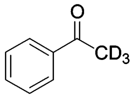
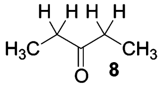
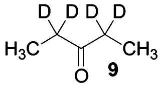
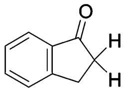
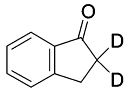
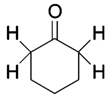
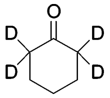


TABLE 5. Deuteration of Various Ketones by Use of VAp Catalyst and D_2O[a]

entry	substrate	product	isotopic [D]:[H] ratio (%)[b]	
			first run	second run
1			90	100 (89)
2			94	100 (86)
3[c]			91	100 (94)
4			79	98 (88)

[a] Substrate (5 mmol), VAp (0.05 g), D_2O (5 mL), 50 °C, 2 h, Ar. [b] Determined by ^1H NMR. Values in parentheses are isolated yield. [c] THF (2 mL) was used as a cosolvent.

2-benzylphenol was readily obtained from the reaction of **2a** with **5a** in sequential reactions of aldol condensation, dehydration, and isomerization (Scheme 4).

Deuteration in D_2O Using the VAp Catalyst. The absolute and relative rates of many individual chemical proton transfer processes have been well documented; however, the development of an efficient deuterium incorporation procedure is still a challenge. The base-catalyzed H−D exchange reaction of a C−H bond adjacent to a carbonyl group has been widely used for the syntheses of α-deuterated ketones.[33] The results of deuteration of several ketones using D_2O as a deuterium source in the presence of the VAp catalyst are shown in Table 5.

Treatment of 3-pentanone (**7**) with D_2O at 50 °C for 2 h gave deuterated 3-pentanone-2,2,4,4-d_4 (**8**) in 94% yield. Moreover, further treatment of the isolated product with D_2O in the presence of the VAp catalyst under identical conditions gave analytically pure **8**. Even for ketones with relatively high pK_a values, such as acetophenone (pK_a = 24.7), 1-indanone (pK_a = 23.0), and cyclohexanone (pK_a = 26.4), efficient deuteration took place to afford the corresponding labeled products in excellent yields. In the VAp-catalyzed deuteration reaction, the amounts of self-aldol products formed were not determined.

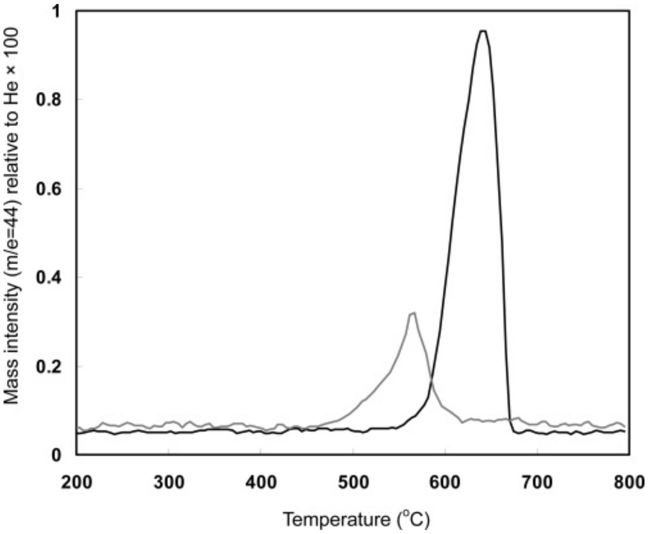


FIGURE 4. TPD plots for CO_2 absorbed on VAp catalysts: VAp calcined at 800 °C, gray line; VAp-hw, black line. Peak intensity is normalized to that of He ($m/e = 4$).

Mechanistic Investigation. After the aqueous Michael reaction of **1a** with **2b** (Table 2, entry 1) and removal of the catalyst by filtration, 7% of Ca leached from the VAp calcined at 800 °C and the XRD spectrum of the catalyst showed the disappearance of the CaO phase (Figure 1f). The Ca/V ratio of the recovered VAp catalyst was determined to be 1.50. It was found that pretreatment with hot water of the VAp calcined at 800 °C, abbreviated as VAp-hw, also led to a reduction of the Ca/V ratio to 1.50 together with the disappearance of the CaO peaks (Figure 1g). Moreover, the BET surface area of the VAp-hw catalyst was found to be 11.6 $m^2 \cdot g^{-1}$, which was similar to that of the spent VAp catalyst. The distribution of calcium and vanadium in the spent VAp was measured by XPS using an etching technique, in which the surface of the spent VAp was composed of a nonstoichiometric phase, while the inner was stoichiometric. Figure 4 shows temperature-programmed desorption (TPD) profiles of carbon dioxide absorbed as a probe on the VAp calcined at 800 °C and the VAp-hw. From the peak positions of the TPD profiles, it can be seen that the surface basicity of the VAp-hw is stronger than that of the VAp calcined at 800 °C. Furthermore, the base amounts in the VAp-hw was approximately 0.32 $mmol \cdot g^{-1}$, which was 2 orders of magnitude greater than that of the VAp calcined at 800 °C (6.6×10^{-3} $mmol \cdot g^{-1}$).

Furthermore, in the reaction of **1a** with **2b**, an addition of 1.5 equiv of benzoic acid based on the amount of surface vanadium species resulted in a significant decrease in product yield from 99% to 37% yield. These results show that *water, when used as a reaction medium, acts as a trigger to generate a nonstoichiometric apatite phase by removal of the CaO phase from the surface, and the distorted vanadate species such as a V−OH species acts as a Brønsted base sites.* As described above, the use of any other organic solvents, e.g. toluene or ethanol, gave no Michael products, and Ca species were not detected in the filtrates. In contrast to the above results, the VAp-hw catalyst promoted the Michael reaction of **1a** with **2a** even in organic solvents (Table 6) such as 1,2-dichloroethane, toluene, and ethanol (entries 2−4). Moreover, in the recycling experiments under aqueous conditions, further Ca dissolution could not be detected in the filtrate.

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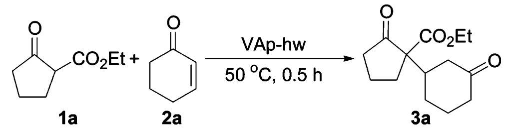
[33] (a) Klei, S. R.; Golden, J. T.; Tilley, T. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 2092. (b) Kingston, L.; Lockley, W. J. S.; Mather, A. N.; Spink, E.; Thompson, S. P.; Wilkinson, D. J. *Tetrahedron Lett.* **2000**, *41*, 2705. (c) Ellames, G. J.; Gibson, J. S.; Herbert, J. M.; Kerr, W. J.; McNeill, A. H. *Tetrahedron Lett.* **2001**, *42*, 6413. (d) Sajiki, H.; Hattori, K.; Aoki, F.; Yasunaga, K.; Hirota, K. *Synlett* **2002**, 1149.

TABLE 6. Michael Reaction of 1a with 2a Catalyzed by VAp-hw[a]



entry	solvent	convn (%)[b]	yield (%)[b]
1	water	>99	>99
2	1,2-dichloroethane	66	66
3	toluene	56	54
4	ethanol	35	33

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), VAp-hw (0.05 g), solvent (3 mL), 50 °C, 0.5 h. [c] Determined by GC using an internal standard technique.

The suggested mechanism of the VAp-catalyzed Michael reaction is as follows. In situ generation of an extremely active V−OH species abstracts an α-proton from the donor to form a 1,3-diketonato vanadium species on the VAp surface. An acceptor subsequently coordinates to a vacant site of the vanadium species through a carbonyl oxygen, and alkylation and hydrolysis then take place, affording the Michael adduct and the regenerated the V−OH species. Such V−OH species can also induce aldol-type condensations and H−D exchange reaction. The hydrophilic nature of the VAp and the structural robustness of the isolated VO$_4$ tetrahedron units on the solid surface offer the possibility of performing diverse array of base-mediated reactions under aqueous conditions.

Conclusions

The VAp, which contains isolated tetrahedral V^{5+} species, has been developed as an extremely active base catalyst for C−C bond-forming reactions such as Michael- and aldol-type reactions under aqueous conditions. Moreover, the VAp was found to be an effective heterogeneous catalyst for the synthesis of α-deuterated ketones using D$_2$O. We continue to refine the catalyst design using apatite components with the aim of developing a range of environmentally benign organic syntheses, including asymmetric reactions.

Experimental Section

Preparation of VAp Catalyst. A mixture of CaSO$_4$•2H$_2$O (11.5 g, 66.8 mmol) and Na$_3$VO$_4$ (7.36 g, 40.0 mmol) in aqueous solution was refluxed for 2 h with excess NaOH (5.0 g). The white slurry was then cooled to room temperature, filtered, washed with large amount of deionized water and dried overnight at 110 °C, followed by calcination at 800 °C for 3 h, yielding the VAp as a white powder. Based on the elemental analysis, the amount of Ca and V were found to be 35.03 and 26.58 wt %, respectively, and the Ca/V ratio of VAp was estimated to be 1.67 in agreement with the stoichiometric value of apatite component.

Typical Procedure for the 200-mmol-Scale Michael Reaction of 1a with 2b in Water (Scheme 2). A mixture of **1a** (32.2 g, 200 mmol), **2b** (15.4 g, 220 mmol), VAp (0.008 g), and water (50 mL) was stirred at 40 °C. After 1.5 h, GC analysis of the supernatant showed complete conversion of **2b**. The reaction mixture was extracted with diethyl ether, washed with brine, and then dried over Na$_2$SO$_4$. Diethyl ether was removed under the reduced pressure, then the residue was distilled to give 41.6 g (92% isolated yield) of analytically pure 2-oxo-1-(3-oxobutyl)-cyclopentanecarboxylic acid ethyl ester (**3b**) as a colorless oil: bp 151−152 °C/6 mmHg; CAS registry number [61771-81-1]; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.25 (t, $J = 7.5$ Hz, 3H), 1.83−2.14 (m, 5H), 2.15 (s, 3H), 2.24−2.50 (m, 4H), 2.71 (ddd, $J = 5$, 9, and 17 Hz, 1H), 4.17 (q, $J = 7.5$ Hz, 2H); ^{13}C NMR (105 MHz, CDCl$_3$) δ 14.5, 20.0, 27.4, 30.3, 34.8, 38.4, 39.3, 59.4, 61.8, 171.8, 208.2, 215.3; IR (neat) 2976, 1747, 1718, 1166 cm^{-1}. HRMS (EI): m/z calcd for C$_{12}$H$_{18}$O$_4$ 226.1205. Found: 226.1182.

A Procedure for the 100-mmol-Scale Aqueous Aldol Reaction (Scheme 3). A mixture of **4a** (11.3 g, 100 mmol), **5a** (11.7 g, 110 mmol), VAp (0.025 g), and water (50 mL) was stirred at 30 °C. The progress of the reaction was monitored by GC analysis. After 5 h, the VAp catalyst was separated from the reaction mixture by a centrifuge. The filtrate was extracted with diethyl ether and then dried over MgSO$_4$. Removal of diethyl ether under the reduced pressure, followed by recrystallization (*n*-hexane and ethyl acetate), afforded analytically pure (2*E*)-2-cyano-3-phenyl- 2-propenoic acid ethyl ester (**6a**) as a white powder (95% isolated yield): CAS registry number [2025-40-3]; mp 52 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.45 (t, 3H, $J = 7.1$ Hz), 4.42 (q, 2H, $J = 7.1$ Hz), 7.48−7.64 (m, 3H), 8.02 (m, 2H), 7.98−8.08 (s, 1H); ^{13}C NMR (105 MHz, CDCl$_3$) δ 14.2, 62.9, 103.7, 115.3, 128.3, 130.3, 132.3, 132.7, 153.6, 162.3; IR (KBr) 1200, 1610, 2240 cm^{-1}. HRMS (EI): m/z calcd for C$_{12}$H$_{11}$NO$_2$ 201.0790. Found: 201.0790.

A Procedure for the Synthesis of 1,3-Dinitro Compounds in Water (Table 4). Into a reaction vessel with VAp (0.05 g), water (5 mL), and nitromethane (1 mL) was added **5a** (1 mmol), and then the resulting mixture was stirred at 110 °C. After 12 h, the VAp catalyst was readily separated from the reaction mixture by a centrifuge. The filtrate was extracted with diethyl ether and then dried over MgSO$_4$. Removal of diethyl ether and nitromethane under the reduced pressure, followed by column chromatography (*n*-hexane/EtOAc = 4/1), afforded analytically pure 2-nitro-1-(nitromethyl)ethylbenzene as a yellow oil (0.19 g, 91% isolated yield): CAS registry number [117538-84-8]; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.22−4.33 (m, 1H), 4.69−4.82 (m, 4H), 7.17−7.20 (m, 2H), 7.22−7.38 (m, 3H); ^{13}C NMR (105 MHz, CDCl$_3$) 42.0, 77.0, 127.6, 129.3, 129.7, 134.5; IR (KBr) 1736, 1560, 1654, 3034 cm^{-1}. HRMS (EI): m/z calcd for C$_9$H$_{10}$N$_2$O$_4$: 210.0641. Found: 210.0637.

Deuteration of Various Ketones by Use of VAp Catalyst (Table 5). Acetophenone-2,2,2-d_3 (entry 1): CAS registry No. [17537-31-4]. Into a reaction vessel with VAp (0.05 g) and deuterium oxide (5 mL) was placed acetophenone (0.60 g, 5 mmol), and the mixture was stirred at 50 °C under Ar atmosphere. After 2 h, the VAp catalyst was readily separated from the reaction mixture by a centrifuge. The reaction mixture was extracted with diethyl ether. The organic layer was dried over MgSO$_4$, filtered, concentrated, and distilled by Kugelrohr (120 °C/50 mmHg). Acetophenone-2,2,2-d_3 [90% atom D] was obtained. Further treatment of the isolated product with the VAp catalyst and D$_2$O in the same manner gave analytically pure acetophenone-2,2,2-d_3 (0.55 g, 100% atm D, 89% isolated yield). HRMS (EI): m/z calcd for C$_8$H$_5$D$_3$O 123.0760. Found: 123.0747.

Acknowledgment. This work is supported by the Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science, and Technology of Japan and the center of excellence program “Creation of Integrated EcoChemistry” of Osaka University. A part of present experiments were carried out by using a facility in the Research Center for Ultrahigh Voltage Electron Microscopy, Osaka University. We thank Prof. Masaharu Nomura (KEK-PF) for XAFS measurement and Dr. Yusuke Yamada (AIST) for TPD measurement.

Supporting Information Available: General procedures, characterization of the VAp catalyst, product identification, experimental section, and reuse of the VAp catalyst in Michael reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0614745