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Michael reaction of 1,3-dicarbonyls with enones catalyzed by a hydroxyapatite-bound La complex

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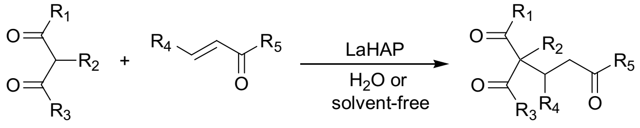
Abstract—A hydroxyapatite-bound La complex, which functioned as an efficient heterogeneous catalyst for the Michael reaction of 1,3-dicarbonyls with enones under aqueous or solvent-free conditions, was prepared using a cation-exchange method. Further application to an asymmetric version by a fluoroapatite-bound La complex catalyst modified with (*R*,*R*)-tartaric acid is also described.

The Michael reaction is widely recognized as one of the most important carbon–carbon bond-forming reactions, leading to functionalized adducts of high synthetic value.[1] In a quest for improving the reaction, various transition metal complexes including chiral version have been developed instead of traditional strong bases.[2] Among them, rare earth metal trifluoromethanesulfonates [RE(OTf)$_3$] are considered to be effective for aqueous Michael reactions.[3] The use of homogeneous metal catalysts, however, is faced with a number of disadvantages including the loss of expensive metals and difficulties in catalysts separation and recovery of the catalysts. In this context, conducting the reaction by heterogeneous catalysts under aqueous or solvent-free conditions instead of using harmful organic solvents could make a contribution to improve environmental outcomes and simplify organic synthesis.[4]

Recently, we disclosed a new strategy for the design of high-performance heterogeneous catalysts utilizing hydroxyapatite (HAP) as a macroligand for catalytically active centers.[5] For example, the cation-exchange ability of the HAP enables an equimolar substitution of Ru^{3+} for Ca^{2+} on their surface, which gives a monomeric Ru^{3+} phosphate species (RuHAP).[5a] This RuHAP could efficiently catalyze the oxidation of alcohols,[5a] amines,[5b] and silanes[5c] under an atmospheric pressure of molecular oxygen. The present work reports the synthesis of a hydroxyapatite-bound La complex (LaHAP) and its evaluation as a recyclable heterogeneous catalyst for the Michael reaction of 1,3-dicarbonyls with enones under aqueous or solvent-free conditions (Scheme 1). We also describe a novel heterogeneous chiral catalyst generated by modification of a fluoroapatite-bound La complex with (*R*,*R*)-tartaric acid (TA-LaFAP). To the best of our knowledge, this is the first demonstration of an asymmetric reaction utilizing an apatite catalyst.[6]

The LaHAP was synthesized according to our previously reported cation-exchange method in an aqueous medium.[5a] Thus, treatment of the stoichiometric hydroxyapatite (2.0 g), $Ca_{10}(PO_4)_6(OH)_2$, with an aqueous solution of La(OTf)$_3$ (1.3×10^{-3} M) at room temperature for 9 h, yielded LaHAP (La content: 0.16 mmol g^{-1}) as a white powder. Characterization by means of XRD, IR, XPS, and La K-edge XAFS proves that a monomeric La^{III} complex surrounded by one



Scheme 1.

Keywords: Michael reaction; 1,3-Dicarbonyls; Heterogeneous catalyst; Lanthanum; Apatite; Asymmetric.

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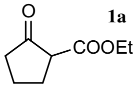
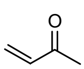
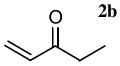
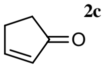
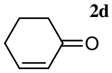
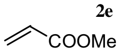
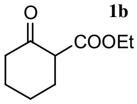
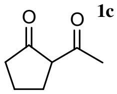
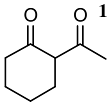
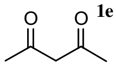
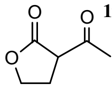
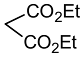
hydroxyl and three weakly coordinated aqua ligands was created on the surface of the HAP.

As can be seen from Table 1, the LaHAP exhibited high catalytic activity for the Michael reaction of 1,3-dicarbonyls with enones under solvent-free (method A) or aqueous conditions (method B), affording the corresponding 1,5-dioxo compounds in excellent yields.[7] In all cases, the desired 1,4-addition products were obtained exclusively without the formation of aldol-type compounds. Acyclic and cyclic enones were found to be good acceptors for the reaction with ethyl 2-oxocyclopentanecarboxylate (**1a**) (entries 1–9). 3-Buten-2-one (**2a**) successfully reacted with a variety of β-keto esters and 1,3-diketones (entries 10–18). Moreover, the LaHAP catalyst was applicable to a less reactive acceptor of methyl acrylate (**2e**) under solvent-free conditions (entry 9). Among the solvents examined, neat and aqueous conditions provided higher yields than those using other organic solvents (58% toluene; 35% acetonitrile; 30% 1,2-dichloroethane; 9% THF; trace amount DMF). It is notable that a 25mmol-scale experiment for **1a** with **2a** was performed to give 90% yield of Michael adduct after 12 h; the corresponding TON and TOF approached 4500 and 375 h^{-1}, respectively.[8] Unfortunately, diethyl malonate (**1g**, $pK_a = 13.3$) proved to be poor donor, affording the corresponding Michael adduct in 65% yield, even when 2.0 mol % La catalyst was employed at 130 °C. The present catalyst also showed specific activity only toward 1,3-dicarbonyls as Michael donors; other active methylene compounds such as ethylcyanoacetate ($pK_a = 9$), which has similar pK_a value to that of acetylacetone (**1e**), did not yield Michael products under identical conditions. Upon completion of the Michael reaction, the LaHAP catalyst was easily separated from the reaction mixture by a sim-

Table 1. Michael reaction catalyzed by LaHAP

Entry	Donor[a]	Acceptor	Method[b]	La (mol %)	Time (h)	Yield (%)[c]
1	 **1a**	 **2a**	A	0.5	0.5	>99
2			B	0.5	0.5	>99
3	**1a**	 **2b**	A	0.5	1	97
4			B	0.5	4	85
5	**1a**	 **2c**	A	1.0	6	86
6			B	1.0	24	89
7[d]	**1a**	 **2d**	A	1.5	13	95
8[d]			B	1.5	27	64
9[d]	**1a**	 **2e**	A	2.0	24	>99
10	 **1b**	**2a**	A	1.0	1	98
11[d]	 **1c**	**2a**	A	1.0	3	97
12[d]			B	1.0	3	99
13[d]	 **1d**	**2a**	A	1.25	6	83
14[d]			B	1.25	24	90
15	 **1e**	**2a**	A	0.5	4	99
16			B	0.5	9	99
17	 **1f**	**2a**	A	0.5	2	95
18			B	0.5	3	99
19[e]	 **1g**	**2c**	A	2.0	24	65

[a] The pK_a values of donors are as follows: **1a** (10.5), **1b** (11.5), **1c** (7.8), **1d** (10.1), **1e** (9.0), and **1g** (13.3).

[b] Method A: donor (2 mmol), acceptor (3 mmol), solvent-free, Ar atmosphere, 50 °C; method B: donor (0.5 mmol), acceptor (0.75 mmol), H_2O (3 ml), Ar atmosphere, 50 °C.

[c] Determined by GC analysis.

[d] 80 °C.

[e] 130 °C.

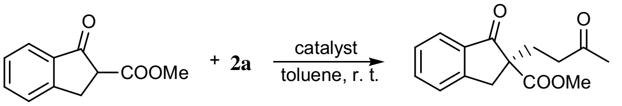
ple filtration using a filter paper. The recovered catalyst was washed with acetone and dried under vacuum at room temperature, which ICP analysis of the filtrate confirmed that the La content was below the detection limit. Moreover, the catalyst was filtered off after ca. 60% conversion at the reaction temperature. Further, treatment of the filtrate under similar reaction conditions did not afford any products. It can be said that the present reaction undoubtedly proceeds on the hydroxyapatite surface, which effectively serves as a promising macroligand for the catalytically active La species.

Treatment of **1a** with D_2O in the presence of the LaHAP led to H–D exchange reaction, giving the α-deuterated compounds in 15% yield.[9] Addition of benzoic acid to the reaction mixture of **1a** with **2a** significantly decreased the catalytic activity. These results demonstrate that the LaHAP has a Brønsted base site, that is, La–OH species.[10] The IR spectrum of the LaHAP upon treatment with **1e** showed a shift of the $\nu(C{=}O)$ band toward 1560 cm^{-1} in comparison with the free carbonyl group at around 1700 cm^{-1}, suggesting the formation of an 1,3-diketonato La species.[11] On the basis of these results, a plausible mechanism is proposed as follows. Initially, a La–OH species abstracts an α-proton of the donor to form a 1,3-diketonato La species. Next, an acceptor coordinate to vacant sites of the La species at the carbonyl oxygen, followed by an alkylation and a hydrolysis to afford a Michael adduct along with the regeneration of the La–OH species. Kinetic studies showed zero-order dependence in **1a** and first-order relationship in **2a**.[12] A k_H/k_D value of 1.0 was also observed in the intermolecular competitive reaction between **1e** and acetylacetone-3,3-d_2($CH_3COCD_2COCH_3$) with **2a** as a Michael acceptor. These results suggest that the alkylation might be a rate-determining step.

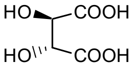
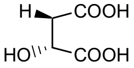
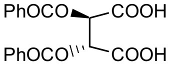
Building upon the initial success of the LaHAP, further investigations were conducted to develop an effective heterogeneous catalyst for the asymmetric Michael reaction.[13] Preliminary screening revealed that the fluoroapatite-bound La complex modified with (*R*,*R*)-tartaric acid (**4a**) (TA-LaFAP; La: 1.2 mol %) in toluene at room temperature efficiently catalyzed the asymmetric Michael reaction of methyl 1-oxoindan-2-carboxylate (**1g**) with **2a**, affording (*S*)-methyl 1-oxo-2-(3′-oxobutyl)-2-indanecarboxylate ((***S***)**-3a**) in 97% yield with a good enantioselectivity of 60% (entry 1 in Table 2).[14] It is noted that the combination of La(OTf)$_3$ and **4a** showed low activity with no enantioselectivity (entry 2). The use of the HAP instead of the FAP gave high chemical yield, but a lower enantioselectivity was obtained with an opposite configuration (entry 3). Among the solvents examined, diethylether and *n*-hexane were good solvents, while dichloromethane and water gave poor results with respect to enantiomeric excess. When the reaction temperature was lowered to 10 °C, the yield significantly decreased to 5% with 40% ee, whereas the reaction at a higher temperature of 40 °C resulted in decrease of enantioselectivity to 50% in spite of high chemical yield (>99%). Other organic modifiers such as (*S*)-malic acid (**4b**) and (*R*,*R*)-*O*,*O*′-dibenzoyltartaric acid (**4c**) favored excess formation of the (*R*)-isomer with moderate enantioselectivity (entries 4 and 5).

In summary, we have developed a method for the design of nanostructured catalysts using apatites. A stable monomeric La phosphate complex on the surface of hydroxyapatite proved to be an efficient heterogeneous catalyst with superior activity for the Michael reaction, and possessed high reusability. Further developments of asymmetric catalysts with enhanced enantioselectivity are now underway.

Table 2. Asymmetric Michael reaction of **1g** with **2a**[a]



1g (***S***)**-3a**

Entry	Catalyst	Ligand	Yield (%)[b]	ee (%)[c]	Confgn.[d]
1	LaFAP	 **4a**	97	60	*S*
2[e]	La(OTf)$_3$		29	<1	*S*
3	LaHAP		>99	30	*R*
4	LaFAP	 **4b**	>99	50	*R*
5	LaFAP	 **4c**	>99	46	*R*

[a] Reaction conditions: catalyst (0.016 g, 1.2 mol % based on **1g**), **1g** (0.5 mmol), **2a** (0.75 mmol), solvent (2 ml), room temperature, 6 h, Ar atmosphere.

[b] Determined by GC.

[c] Determined by HPLC (Daisel Chiralpak AD-H).

[d] Assigned by optical rotation.

[e] La(OTf)$_3$ (3.4×10^{-3} g, 1.2 mol % based on **1g**), **4a** (8.6×10^{-4} g, 1.2 mol % based on **1g**).

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7. The order of activity of various catalysts for Michael reaction conducted under the identical reaction conditions as those for entry 1 in Table 1 was LaHAP (>99) > ScHAP (90) > YHAP (67) > La(OTf)$_3$ (40) > YbHAP (39) > HAP (30), where values in parentheses indicate yields of Michael adducts. The parent HAP is reported to act as a heterogeneous catalyst for the Michael reaction of mercaptans with chalcone derivatives, but it was found to be less effective under the present reaction conditions, see: Zahouily, M.; Abrouki, Y.; Bahlaouan, B.; Rayadh, A.; Sebti, S. *Catal. Commun.* **2003**, *4*, 521.
8. Into a reaction vessel equipped with a reflux condenser were successively placed the LaHAP (0.03 g, La^{3+}: 0.02 mol %), H$_2$O (20 ml), **1a** (25 mmol), and **2a** (37.5 mmol). The reaction mixture was stirred at 80 °C under an Ar atmosphere for 12 h. After separation of the catalyst, the aqueous layer was extracted with Et$_2$ O and organic solvent was dried with MgSO$_4$. The solvent was evaporated and the crude product was distilled to afford pure ethyl 2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate as a colorless oil (90% isolated yield).
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12. The kinetic results are in sharp contrast to those of homogeneous La(OTf)$_3$ catalysts, which follow first-order dependence in **1a** and zero-order relationship in **2a**. We believe this phenomenon can be attributed to strong Brønsted basicity of the LaHAP catalyst.
13. For general reviews of catalytic asymmetric Michael reactions, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171; (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.
14. Into a reaction vessel were successively placed the TA-LaFAP (0.016 g, La^{3+}: 1.2 mol %), toluene (2 ml), **1g** (0.5 mmol), and **2a** (0.75 mmol). The reaction mixture was stirred at room temperature under an Ar atmosphere for 6 h. After removal of the catalyst, the reaction mixture was diluted with toluene and subjected to HPLC analysis. The enantiomeric excess was determined by chiral HPLC (Daisel Chiralpak AD-H, eluent: ^{i}PrOH/hexane = 1:9, flow rate: 1.0 ml/min, 254 nm, t_R of (*S*)-**3a** = 12.0 min, t_R of (*R*)-**3a** = 13.5 min). The absolute configuration was determined by the optical rotation of **3a** $[\alpha]_D^{25}$ −41.8 (*c* 0.24, benzene) for 60% ee, cf.: $[\alpha]_{578}^{rt}$ −77.0 (*c* 2.0, benzene) for (*S*)-isomer. Preparation of the TA-LaFAP was accomplished as follows. To a stirred aqueous solution of 1:1 of La(OTf)$_3$ and (*R*,*R*)-tartaric acid for 30 min was added a fluoroapatite (FAP), Ca$_{10}$(PO$_4$)$_6$F$_2$, and then the mixture was further reacted at 30 °C for 24 h, affording the TA-LaFAP (La content: 0.36 mmol g^{-1}) as a white powder. The ratio of La:TA was determined to be ca. 6:1 by the CHN elemental analysis.