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Transesterification Reactions Catalyzed by a Recyclable Heterogeneous Zinc/Imidazole Catalyst

Daiki Nakatake,[a] Ryo Yazaki,[a] Yoshimasa Matsushima,[b] and Takashi Ohshima[a,*]

[a] Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi Higashi-ku, Fukuoka 812-8582, Japan
Fax: (+81)-092-642-6654; phone: (+81)-092-642-6650; e-mail: ohshima@phar.kyushu-u.ac.jp
[b] Corporate Research and Development Division, Takasago International Corporation, 1-4-11 Nishi-yawata, Hiratsuka, Kanagawa 254-0073, Japan

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Abstract: We report the development of a universal and recyclable heterogeneous zinc/imidazole catalyst. The catalyst is recoverable through simple filtration and can be reused at least five times, retaining its catalytic activity. Leached zinc species were not responsible for the observed catalysis based on the hot filtration test and ICP-MS analysis. The heterogeneous zinc catalyst also promotes chemoselective transesterification over amidation.

Keywords: chemoselective process; heterogeneous catalysis; recyclable catalyst; transesterification; zinc

Esters are a common functional group found in natural products, drugs, and functional materials.[1] For the industrial scale production of esters, catalytic transesterification of lower esters is a highly advantageous method due to its high atom-economy compared with traditional methods using carboxylic acids under stoichiometric amounts of condensation reagents or highly reactive acyl chlorides or anhydrides.[2] In addition, transesterification can be performed under almost neutral conditions, allowing for high functional group compatibility. Considerable research efforts are therefore devoted to the development of robust and practical catalysts for transesterification, especially heterogeneous catalysts. Heterogeneous catalysts have several advantages, including high stability, reusability, and turnover number (TON), and ease of product purification.[3] Several metal oxides or doped metal oxides, such as CaO,[4] MgO,[5] ZrO_2,[6] SnO_2[7] and zeolite,[8] have been used as heterogeneous catalysts for transesterification. Although these metal oxide catalysts are inexpensive and recyclable, they have narrow functional group compatibility due to their inherent acidic or basic character. Thus, the development of alternative heterogeneous transesterification catalysts that operate under milder conditions is in great demand.

We previously reported that combined use of μ-oxo-tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$ (**1**)[9] (Figure 1) with a catalytic amount of *N*-heteroaromatic compounds, such as DMAP, significantly facilitated

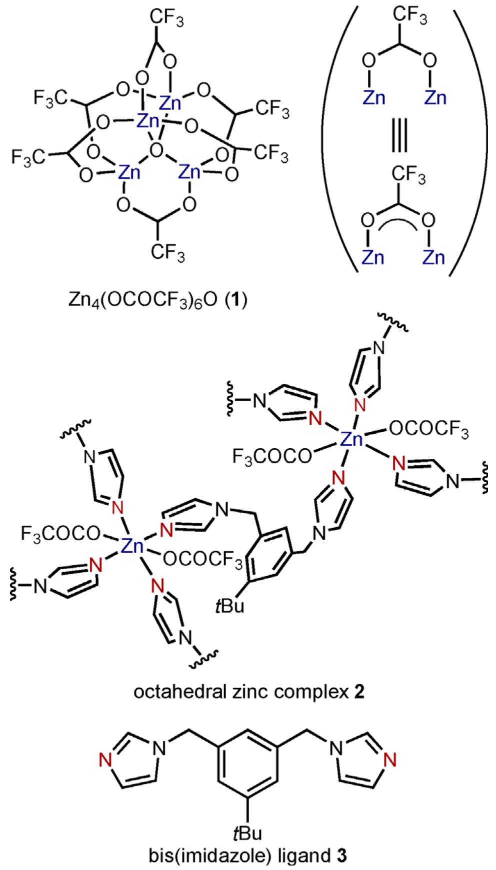


Figure 1. The structures of $Zn_4(OCOCF_3)_6O$ (**1**) and octahedral zinc complex **2** prepared from $Zn(OCOCF_3)_2$ and bis(imidazole) ligand **3**.

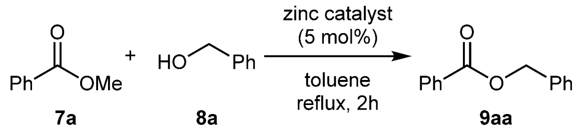
the transesterification reaction rate through *in situ* generation of more active lower-nuclear Zn species.[9c] Moreover, we recently developed the highly reactive octahedral zinc complex **2** supported by a designed bis(imidazole) ligand **3**.[10] The high stability of zinc complex **2** enabled the practical use of **2** for transesterification reactions without strict concern regarding air and moisture. The highly crystalline nature of **2** stemming from its infinite network structure, however, limits the applicability of **2** in organic solvents. Herein we report the development of a practical and recyclable zinc/imidazole catalyst immobilized on polystyrene resin as a highly active and chemoselective heterogeneous catalyst for transesterification and transcarbonation reactions in a variety of organic solvents.

As shown in Scheme 1, imidazole is readily attached to a commercially available cross-linked Merrifield resin **4** (Cl loading = 2.40 mmol g^{-1}) under standard basic conditions. The imidazole content of resin **5** was determined to be 1.99 mmol g^{-1} by elemental analysis. For complexation of imidazole resin **5** and zinc salt, the zinc/imidazole ratio and solvent selection were crucial for obtaining high catalytic activity.[11] The use of four equivalents of imidazole to zinc ions under THF reflux conditions was optimal, and the zinc content of **6** was determined to be 0.399 mmol g^{-1} by ICP-MS analysis. We also investigated the immobilization of a previously developed *m*-substituted bis(imidazole) unit[10] on Merrifield resin in place of an imidazole unit, but the catalytic activity was much lower than that of zinc/imidazole catalyst **6**.[11] In addition, a silica-gel supported imidazole ligand gave only unsatisfactory results.[11]

With newly prepared heterogeneous zinc/imidazole catalyst **6** in hand, **6** and other zinc catalysts were applied to transesterification in toluene for a short reaction time (Table 1). Both $Zn(OCOCF_3)_2$ and $Zn_4(OCOCF_3)_6O$ afforded the product **9aa** in low yield (entries 1 and 2). Our developed zinc/bis(imidazole) complex **2**, which potentially has higher catalytic activity than $Zn_4(OCOCF_3)_6O$, also exhibited poor catalytic performance due to its low solubility in toluene (entry 3). The combined use of $Zn(OCOCF_3)_2$ and *N*-methylimidazole (NMI) (zinc/NMI = 1/4) showed a high catalytic performance (entry 4). The newly developed heterogeneous zinc/imidazole catalyst **6** was completely insoluble during the course of the reaction, but had comparable catalytic performance as the homogeneous zinc/NMI catalyst, and product **9aa** was observed in 97% yield (entry 5).[12] No product was observed by using imidazole resin **5** (entry 6).

Scheme 1. Preparation of heterogeneous zinc/imidazole catalyst **6**.

Table 1. Evaluation of zinc catalysts.[a]



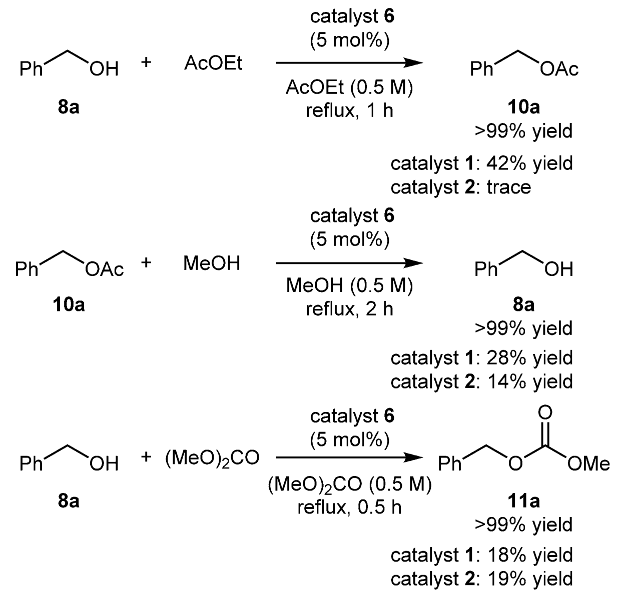
Entry	Zinc catalyst	Yield [%]
1	$Zn(OCOCF_3)_2$	19
2	$Zn_4(OCOCF_3)_6O$ (**1**)	21
3	zinc/bis(imidazole) complex (**2**)	38
4	$Zn(OCOCF_3)_2$ + NMI[b]	97
5	heterogeneous zinc/imidazole catalyst (**6**)	97
6	imidazole resin (**5**)	N.D.

[a] *Reaction conditions:* **7a** (0.5 mmol), **8a** (0.6 mmol), toluene (1.0 mL), reflux (oil bath temp. = 120 °C). Yields were determined by GC analysis using nonadecane as an internal standard.

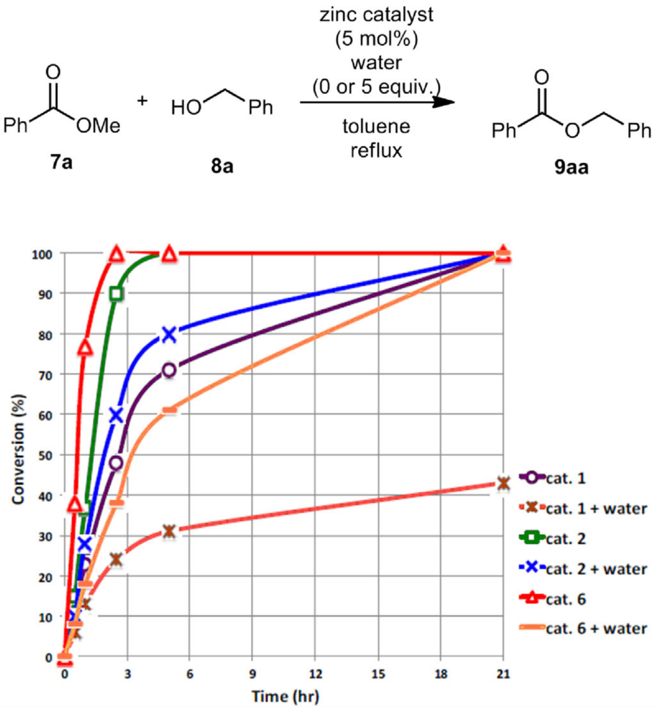
[b] NMI = *N*-methylimidazole.

To confirm further applicability of our heterogeneous zinc/imidazole catalyst **6** in various other reactions (solvents), we next examined the reaction scope (Scheme 2). While heterogeneous zinc/imidazole catalyst **6** was insoluble in all solvents, catalyst **6** effectively delivered the desired products quantitatively in all the reactions: acetylation in ethyl acetate, deacetylation in methanol, and methoxycarbonylation in dimethyl carbonate,[13] within a short reaction time. When other zinc catalysts shown in Table 1 were used, lower yields were obtained, except for a homogeneous catalyst comprising $Zn(OCOCF_3)_2$ and NMI (up to 42% yield, see the Supporting Information for details), thus highlighting the wide applicability of the present heterogeneous catalyst **6**.

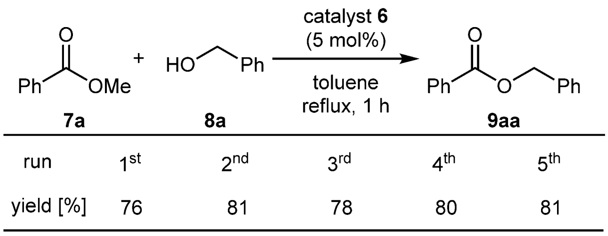
We evaluated the stability of the present heterogeneous catalyst **6** by water-addition control experiments (Scheme 3).[10] In the presence of five equivalents of water, $Zn_4(OCOCF_3)_6O$ (**1**) provided the product **9aa** in moderate yield even after prolonged reaction time. In sharp contrast, heterogeneous zinc catalyst **6** afforded similar results as the previously de-



Scheme 2. Reaction scope using heterogeneous zinc/imidazole catalyst **6**.



Scheme 3. Reaction profiles in the presence of water.



run	1st	2nd	3rd	4th	5th
yield [%]	76	81	78	80	81

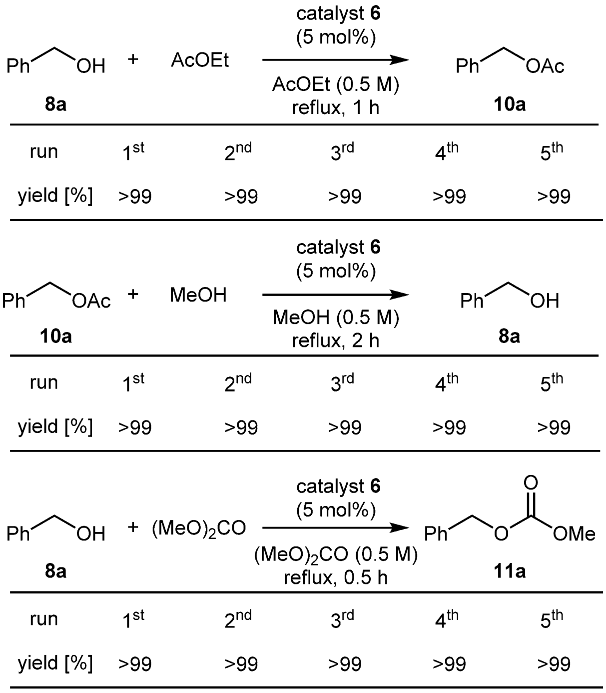
Scheme 4. Recovery and recuse experiments.

veloped highly stable zinc complex **2** and the product **9aa** was obtained in quantitative yield after 21 h, demonstrating that the high stability of the present heterogeneous catalyst **6**.

Because the present heterogeneous zinc catalyst **6** was highly stable, **6** was storable on the bench without strict concern regarding air and moisture, and after the reaction catalyst **6** was easily recovered through simple filtration.[11] Therefore, to demonstrate the recyclability of heterogeneous zinc/imidazole catalyst **6**, recovery-reuse experiments were performed (Scheme 4). To measure the catalytic activity, each reaction was quenched after 1 h with ~80% yield (prolonged reaction time resulted in the completion of the reactions, >99% yield). The simply recovered heterogeneous zinc catalyst **6** retained high catalytic activity, even after five runs (76%–81% yield).

The recyclability of heterogeneous zinc catalyst **6** was also demonstrated in acetylation, deacetylation, and transcarbonation (Scheme 5). In all the reactions, complete conversions were observed after five runs and catalytic activity was retained. It is noteworthy that significant deactivation was not observed, even when using highly coordinative alcohol as the solvent, verifying the wide solvent tolerance of catalyst **6**.

To confirm that the insoluble catalyst promotes the reaction under heterogeneous conditions, we conduct-



run	1st	2nd	3rd	4th	5th
yield [%]	>99	>99	>99	>99	>99

run	1st	2nd	3rd	4th	5th
yield [%]	>99	>99	>99	>99	>99

run	1st	2nd	3rd	4th	5th
yield [%]	>99	>99	>99	>99	>99

Scheme 5. Recovery and recuse experiments in various reactions.

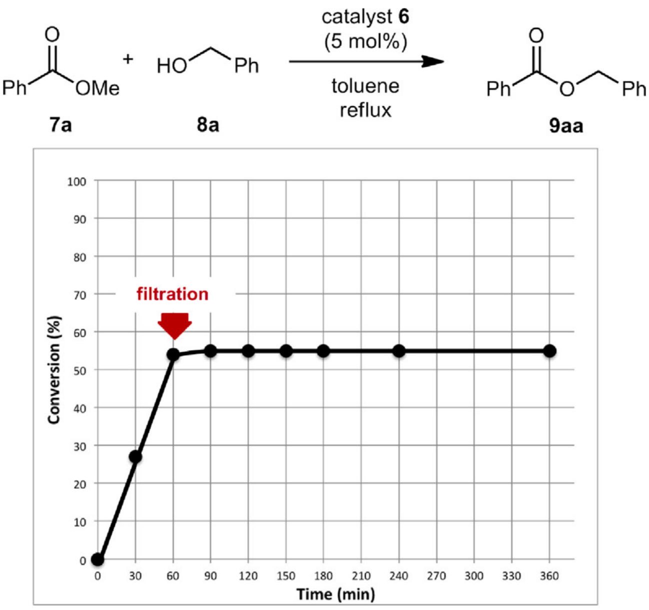
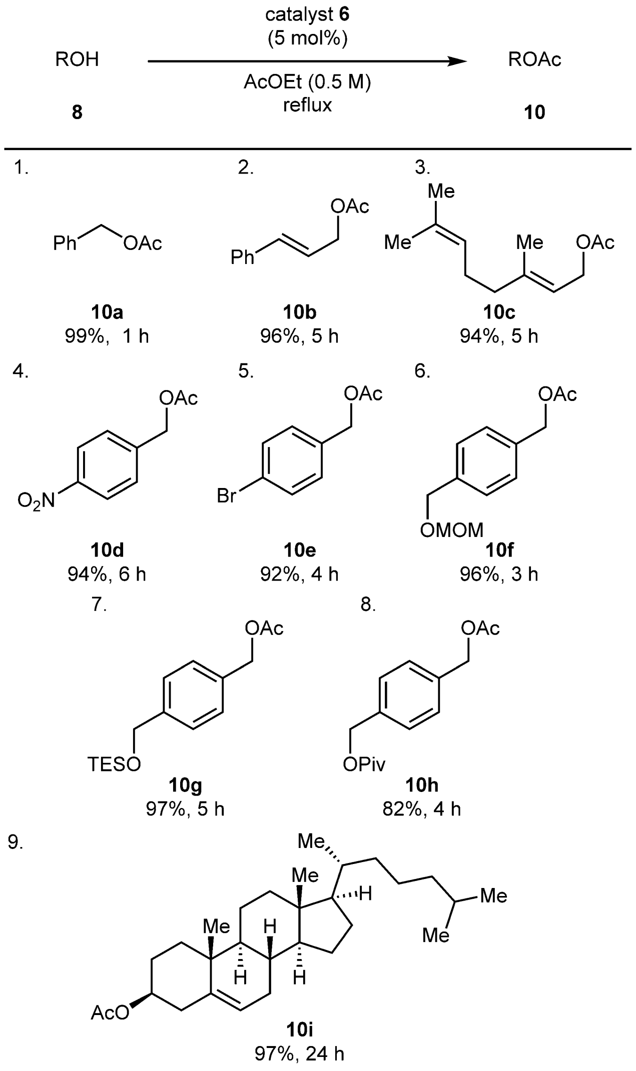
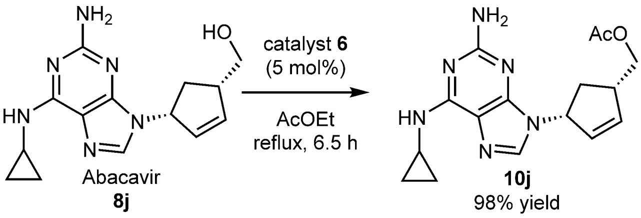


Figure 2. Hot filtration test.

Table 2. Substrate scope in acetylation.[a]



[a] *Reaction conditions:* **8** (1.0 mmol), EtOAc (2.0 mL), 90 °C. Isolated yields are shown.

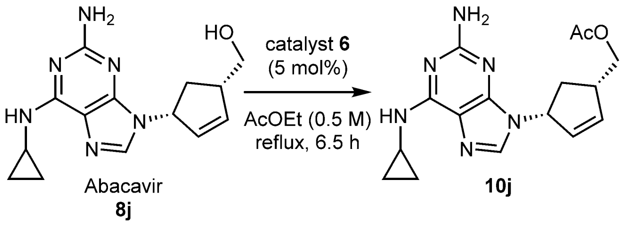


Scheme 6. Chemoselective acetylation of abacavir (**8j**).

ed a hot filtration test. The heterogeneous reaction mixture was filtered to remove catalyst **6** after 60 min (54% conversion), and the resulting filtrate was further heated under reflux conditions. Even after an additional 300 min, however, conversion to the product **9aa** remained unchanged, suggesting that leached zinc species did not catalyze the reaction at all (Figure 2).[14]

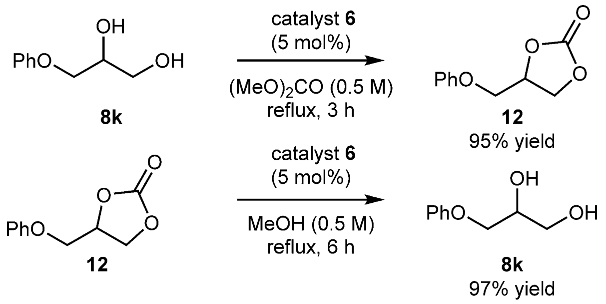
We next investigated the substrate scope in an acetylation reaction (Table 2), which cannot be catalyzed by the previously developed poorly soluble zinc/bis-(imidazole) complex **2**. Cinnamyl alcohol (**8b**) and geraniol (**8c**) were smoothly converted into the corresponding acetates in high yield (entries 2 and 3).[15] Nitro and bromo groups were tolerated during the reactions and the desired products were obtained in excellent yield (entries 4 and 5). The mildness of the present catalysis was demonstrated by using substrates with a variety of protecting groups (MOM, TES, Piv) (entries 6–8). A secondary alcohol on cholesterol was applicable with a prolonged reaction time (entry 9). High functional group compatibility was highlighted by using abacavir (**8j**), an antiretroviral medication for the prevention and treatment of HIV/AIDS. The *O*-acetylation of abacavir (**8j**) was achieved chemoselectively over *N*-acetylation and the desired product **10j** was isolated in 98% yield (Scheme 6). This result clearly suggested that heterogeneous zinc catalyst **6** can be applied to chemoselective transesterification of amino alcohol over amidation.[11,16] We next checked the recyclability of the present heterogeneous catalyst **6** on chemoselective acetylation of highly coordinative abacavir (**8j**) (Scheme 7). Recovery-reuse experiments of chemoselective reactions using highly coordinative amino alcohols remain a difficult task. Although a decreased catalytic activity was observed after the fourth run, the catalyst could be used at least three times without significant loss of activity at this stage.

Finally, we applied the present zinc catalysis to a protection-deprotection sequence of a 1,2-diol



run	1st	2nd	3rd	4th	5th
yield [%]	98	97	93	73	42

Scheme 7. Recovery and recuse experiments using highly coordinative abacavir (**8j**).



Scheme 8. Protection-deprotection sequence of a 1,2-diol through transcarbonation.

through transcarbonation (Scheme 8). 1,2-Diol **8k** was cleanly converted into cyclic carbonate **12** in high yield using dimethyl carbonate through intramolecular transcarbonation.[10,13b] In the reverse direction, cyclic carbonate **12** was converted into 1,2-diol **8k** by changing the solvent to methanol. These results demonstrate that catalyst **6** could be used for the protection/deprotection of 1,2-diols under almost neutral conditions without any acid or base.[10]

In conclusion, we developed highly practical heterogeneous zinc/imidazole catalyst **6**. Catalyst **6** was effective in a broad spectrum of solvents, such as toluene, ethyl acetate, methanol, and dimethyl carbonate, with enhanced catalytic activity. The recyclability of catalyst **6** was also demonstrated by recovery-reuse experiments, and catalyst **6** promoted various reactions in various solvents at least five times without loss of the activity. Studies on the further application of the heterogeneous zinc catalyst to a continuous flow process are in progress.

Experimental Section

General Procedure for Transesterification Reactions

An oven-dried Schlenk flask equipped with a magnetic stirring bar and reflux condenser was charged with zinc catalyst (5.0 mol% zinc). Solvent (2.0 mL) was added to the flask *via* syringe, followed by the addition of starting materials (1.0 mmol) at room temperature. The reaction mixture was then heated under an argon atmosphere. The resulting crude reaction mixture was applied to GC analysis or purified flash column chromatography to determine the product yield.

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[11] See the Supporting Information for details.
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[14] We also measured the zinc ion content after the reaction by ICP-MS analysis and found that only 0.3% of zinc ion was detected in the filtrate.
[15] When acetylated products **10b** and **10c** were also subjected to the deacetylation conditions in methanol, quantitative conversions were observed. In addition, methoxycarbonated products were cleanly obtained using cinnamyl alcohol (**8b**) and geraniol (**8c**). See the Supporting Information for details.
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