






Vigorously stirred La_2O_3 suspensions for Michael additions in water†

Cite this: DOI: 10.1039/d4cc02343a

 Received 14th May 2024,
Accepted 13th August 2024

DOI: 10.1039/d4cc02343a

rsc.li/chemcomm

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This work demonstrates the effectiveness of vigorously stirred lanthanum oxide (La_2O_3) suspensions in catalyzing Michael additions in water. These surfactant-free suspensions offer a counterintuitive yet highly efficient approach compared to traditional methods. Notably, the reactions are ineffective in the absence of water, suggesting a crucial role for the aqueous environment.

The emergence of water as an eco-friendly solvent in synthetic chemistry is driven by its ability to speed up reactions and control selectivity exceptionally well.¹ Organic reactions using only water as a reaction medium can be classified into three main categories (Type I, II, and III) according to the solubility of the reactants and can be further subdivided into two or three categories according to the solubility of the catalyst. Notably, surfactant-based techniques (Type II reactions) have bridged the gap between traditional organic chemistry using organic solvents and water-based reactions.² Surfactants address the inherent solubility challenges of organic compounds in water. Over the past few decades, numerous catalytic systems have been developed and used in surfactant solutions. However, a surfactant-free approach (Type III reactions) has emerged as a preferred alternative, moving beyond the traditional “solution chemistry” paradigm and eliminating the need for bulk reactant dissolution.^{3–6} This shift has led to a growing interest in type IIIc reactions,³ where reactants, catalysts, and water are immiscible. Amazingly, even solid–solid–water ternary mixtures can be employed in these reactions. This counterintuitive phenomenon highlights the limitations of our current understanding of reaction efficiency.

Metal oxides are widely used as solid catalysts in organic synthesis due to their versatile properties: acid–base and redox activity, strong stability, and abundance.⁷ However, their

potential for aqueous organic reactions remains largely untapped, despite promise in water splitting.⁸ We propose exploiting the acid–base properties of metal oxides for type IIIc reactions. As a model, we studied the Michael addition of ethyl acetoacetate (**1a**) to water-insoluble enones, using rare earth oxides as catalysts. Notably, **1a** has a lower $\text{p}K_{\text{a}}$ and significantly lower nucleophilicity in water compared to DMSO due to hydration ($\Delta\text{p}K_{\text{a}}$ –3.5, $\Delta\text{nucleophilicity}$ –8.65).⁹ We propose that interfacial reactions on metal oxide surfaces under type IIIc conditions can create an environment that facilitates deprotonation, nucleophilic addition, and protonation by strategically manipulating hydration (Fig. 1). In this scenario, the deprotonated form of **1a** (**1a[–]**), favored in water, would experience enhanced nucleophilicity upon interacting with the water-insoluble enone. This effect would be further amplified by the acidic nature of the metal oxide surface. Finally, water can facilitate protonation to form the Michael adduct.

Our screening of various metal oxides identified lanthanum oxide (La_2O_3)¹⁰ as the most effective catalyst (Table 1a). An aqueous solution of NaOH yielded only a small amount of the Michael adduct (3% after 24 hours), highlighting the crucial role of acidity of the catalyst. While La_2O_3 is known to readily absorb moisture and convert to lanthanum hydroxide ($\text{La}(\text{OH})_3$), $\text{La}(\text{OH})_3$ exhibited negligible catalytic activity (entry 3). Furthermore, water proved to be the superior reaction medium, despite **2a** not being soluble in water (Table 1b). Reactions conducted in

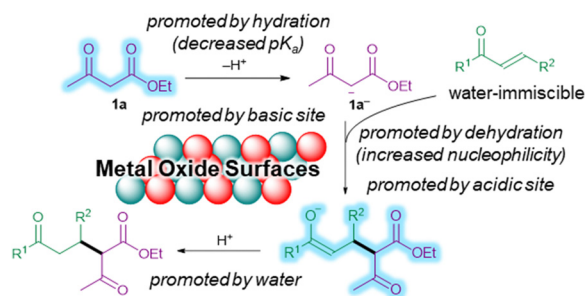


Fig. 1 Concept of hydration-controlled Michael addition of **1a** catalyzed by acidic/basic sites on metal oxide surfaces.

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4cc02343a>

Table 1 Optimization studies

(a)

| Entry | Catalyst | Yield ^a (%) |
|-------|---------------------------------|---------------------------|
| 1 | Sc ₂ O ₃ | NR ^b |
| 2 | Y ₂ O ₃ | 11 |
| 3 | La ₂ O ₃ | 90 (trace) ^{b,c} |
| 4 | CeO ₂ | NR ^b |
| 5 | Pr ₆ O ₁₁ | 7 ^b |
| 6 | Nd ₂ O ₃ | 38 |
| 7 | Sm ₂ O ₃ | 47 |
| 8 | Eu ₂ O ₃ | 38 |
| 9 | Gd ₂ O ₃ | 31 |
| 10 | Tb ₄ O ₇ | NR ^b |
| 11 | Dy ₂ O ₃ | 12 |
| 12 | Ho ₂ O ₃ | 11 ^b |
| 13 | Er ₂ O ₃ | NR ^b |
| 14 | Tm ₂ O ₃ | 7 ^b |
| 15 | Yb ₂ O ₃ | 4 |
| 16 | Lu ₂ O ₃ | 1 |

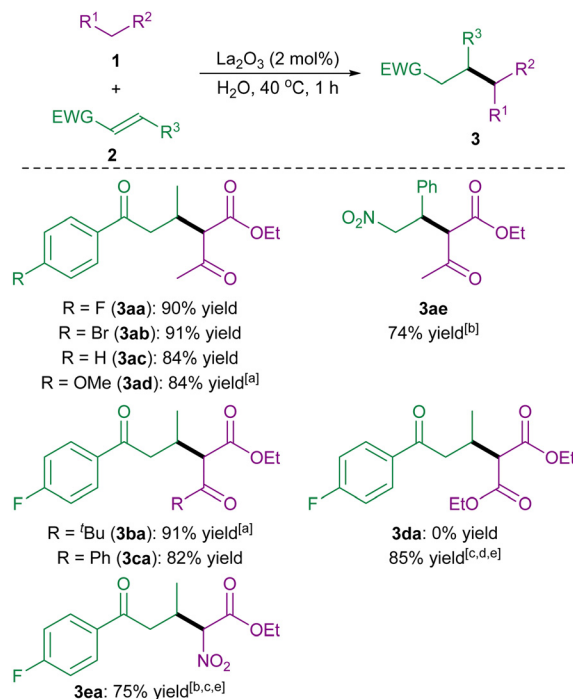
(b)

| Entry | Medium | Yield ^d (%) |
|-------|---------------------------------|------------------------|
| 1 | H ₂ O | 90 (66) ^e |
| 2 | ⁿ hexane | Trace |
| 3 | CH ₂ Cl ₂ | Trace |
| 4 | THF | Trace |
| 5 | DMSO | Trace |
| 6 | MeOH | 4 |
| 7 | EtOH | 1 |
| 8 | – (neat) | 2 |

^a Determined by ¹H NMR analysis. ^b Run for 2 hours. NR = No reaction. ^c La(OH)₃ was used instead of La₂O₃. ^d Determined by ¹H NMR analysis. ^e Run in D₂O.

organic solvents or a solvent-free environment produced a minimal quantity of product, while vigorous stirring in a solid–oil–water suspension significantly accelerated the reaction. The lower concentration of the enol form of reactant **1a** in water compared to organic solvents suggests minimal involvement of the enol form.¹¹ The slower reaction rate observed in deuterium oxide corroborates the role of water in the final protonation step (entry 1).

This unique water-upregulated catalysis on solid surfaces encouraged us to explore a broader range of substrates (Scheme 1). α,β -Unsaturated ketones reacted well with **1a**, although electron-rich acceptors displayed slightly lower reactivity.

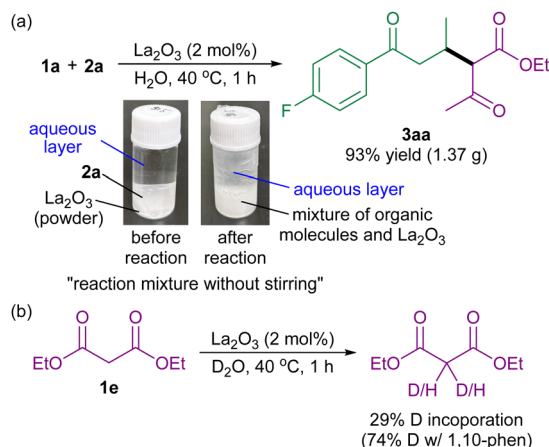


Scheme 1 Scope of La₂O₃-catalyzed Michael addition run under type IIIc conditions. ^a Run for 2 hours. ^b Run for 24 hours. ^c La₂O₃ (5 mol%) was used. ^d Run for 5 hours. ^e 1,10-phen (6 mol%) was added.

Notably, solid β -nitrostyrene (**2e**) functioned as a viable Michael acceptor. Interestingly, the optimal conditions were unaffected by lipophilic β -ketoesters (**1b**, **1c**). Malononitrile (**1d**) also proved to be a suitable pronucleophile. Subsequently, we focused on expanding the scope to include more challenging pronucleophiles. Diethyl malonate (**1e**), with its lower acidity,⁹ failed to react under standard conditions. The combination of La₂O₃ and 1,10-phenanthroline (1,10-phen) fortuitously promoted the reaction (see ESI† for details). This highlights the intriguing possibility of enhancing catalyst performance by decorating solid surfaces with water-soluble modifiers. Furthermore, this combined catalyst system enabled the use of the less nucleophilic⁹ ethyl α -nitroacetate (**1f**), a masked amino acid.

The gram-scale reaction in Scheme 2a highlights the robustness and scalability of this protocol. Three distinct phases are readily observable: liquid Michael acceptor **2a** forms a lower layer beneath the aqueous phase, while solid La₂O₃ precipitates as a separate layer. Vigorous stirring disperses **2a** into small droplets and pulverizes La₂O₃ into a fine powder. Following one hour of stirring, the organic layer containing the reaction product separates spontaneously from the aqueous layer.

To clarify the role of La₂O₃ in carbanion formation, control experiments were conducted using deuterium oxide (D₂O) (Scheme 2b). We employed compound **1e** to prevent participation of the enol form. Vigorous stirring of a biphasic mixture of **1e** and D₂O at 40 °C resulted in minimal deuterium incorporation (<10%). In contrast, a suspension containing La₂O₃, **1e**, and D₂O significantly increased the amount of deuterium at the α -position to 30%. Furthermore, in the presence of 1,10-phen,



Scheme 2 (a) Scale-up synthesis using solid–oil–water suspensions. (b) Deuterium exchange experiments using La₂O₃ in D₂O.

three-quarters of the α -proton were replaced with deuterium. This observation confirms that La₂O₃ promotes both carbanion formation and its subsequent reaction with the Michael acceptor. In addition, it suggests that 1,10-phen plays a prominent role in increasing the nucleophilicity of the carbanion as well as facilitating the carbanion formation.

In conclusion, vigorously stirred La₂O₃ suspensions in water demonstrated exceptional efficiency (e.g., high yields, short reaction times) for carbon–carbon bond formation. Water proved irreplaceable by organic solvents in this system. Beyond the advantages of aqueous environments (lower pK_a values, faster proton transfer), the synergy between acidic and basic nature of La₂O₃ further accelerates the reaction. The protocol is operationally simple and scalable. These findings highlight the potential of water-based organic reactions to unlock a vast array of unexplored reactivities.

This work was supported by a Grant-in-Aid for Science Research (JP22H04972 to T. K., Y. Y., S. K.) from the Japan Society for the Promotion of Science (JSPS).

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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