Green Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2025, **27**, 7960

"On-seawater" accelerated aquacatalysis by edible fatty acids: harnessing the remarkable salting-out effect†

Soo Bok Kim,[a] Seok Ju Hong,[a] Dong Hyeon Kim,[a] Gang Min Lee,[a]‡ Yujin Lim,[b] Sangkyu Lee,[b] Yongseok Kwon[b] and Han Yong Bae*[a]

Medium-chain fatty acids (MCFAs) are widely recognized for their metabolic and therapeutic benefits, yet their potential as catalysts for chemical reactions remains elusive. Herein, we report the development of a sustainable aquacatalytic system utilizing MCFAs, particularly caprylic acid, for Brønsted acid-catalyzed carbonyl allylation under "on-water" conditions. This approach leveraged the salting-out effect induced by NaCl to suppress micelle formation and enhance interfacial catalysis. By employing unrefined seawater and edible sea salt as cost-effective additives, the system enables the efficient allylation of aldehydes without a catalyst and the caprylic acid-catalyzed allylation of ketones. This reaction is scalable to gram-scale synthesis using a chromatography-free purification process, offering a practical and sustainable route for producing active pharmaceutical ingredients. Furthermore, the mild reaction conditions and compatibility with aqueous media facilitated successful on-DNA allylation, underscoring the potential of DNA-encoded library applications in drug discovery. This study highlights the unprecedented utility of MCFAs as renewable catalysts and establishes a versatile and environmentally friendly platform for aquatic organic transformations.

Received 24th March 2025,
Accepted 2nd June 2025

DOI: 10.1039/d5gc01441g

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1. This study introduces a new sustainable aquacatalytic system utilizing medium-chain fatty acids (MCFAs), especially caprylic acid, for Brønsted acid-catalyzed carbonyl allylation under "on-water" conditions. The system operates efficiently using seawater or edible sea salt, offering a low-cost and environmentally benign alternative to conventional solvent systems.
2. The core innovation exploits the salting-out effect to suppress micelle formation and enhance interfacial reactivity, enabling catalyst-free aldehyde allylation and caprylic acid-catalyzed ketone allylation in aqueous media. The reaction conditions are mild, scalable, and compatible with DNA-tagged substrates, opening avenues for pharmaceutical synthesis and drug discovery.
3. Future directions may involve broadening the scope of MCFA-based catalysis across other aqueous transformations, integrating renewable MCFA sources from food or waste streams, and developing entirely water-based catalytic platforms to further enhance the system's green chemistry potential.

Introduction

Medium-chain fatty acids (MCFAs), which are carboxylic acids with carbon chain lengths of 6–12, are rapidly digested and absorbed by the human body and serve as an efficient energy source.[1–4] In addition to their metabolic roles, MCFAs offer a range of health benefits, including weight loss support,[5–7] reduction in cardiovascular disease risk,[8] enhancement of diet-induced thermogenesis and satiety,[9] antimicrobial activity,[10] and improved digestive efficiency.[11] These unique properties have garnered significant attention in nutritional science and medical research, as they are valuable components in functional foods and therapeutic interventions.[3,12–14] In addition to their biological significance, MCFAs exhibit distinctive amphiphilic properties owing to their chemical structure, which features a hydrophilic head and a hydrophobic tail. This structure imparts surfactant-like characteristics, including excellent biocompatibility, biodegradability, low toxicity, and high specificity. These characteristics make MCFAs suitable for applications such as drug delivery systems in both synthetic and biomedical contexts.[15] Notably, in aqueous environments, MCFAs can self-assemble into micelles at their critical micelle concentration (CMC), which enables them to perform stably and efficiently under physiological conditions.[16,17] Caprylic acid (C8:0), a prominent MCFA, exem-

[a]*Department of Chemistry, Sungkyunkwan University, Suwon, 16419, Republic of Korea. E-mail: hybae@skku.edu*
[b]*School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea*
†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d5gc01441g
‡Present address: RIST, Gwangyang, Jeollanam-do, 57801, Republic of Korea.

plifies the advantages of this class of compounds. The carbon chain enhances its solubility and metabolic efficiency, facilitating its rapid absorption and direct utilization as an energy source in the liver.[18] In addition, its potent antimicrobial activity against various pathogens underscores its utility in functional foods and therapeutic applications.[10] Furthermore, their ability to form stable micelles highlights their potential as versatile carriers.[19,20] However, their role as catalysts in chemical reactions remains entirely elusive (Fig. 1A).

Recent studies by our group have revealed that various catalytic transformations can be effectively accelerated under "on-water" conditions,[21–25] where reactions occur at the interface between bulk-water and compact-oil phases.[26,27] Mechanisms such as the use of Brønsted superacids[21] and Brønsted superbases,[22,24] and photocatalysis[25] were observed, which significantly augmented the catalytic activity at the interface.[28] This phenomenon is mainly observed in addition-type reactions (*e.g.*, Michael addition and [2 + 2] cycloaddition), which typically involve a decrease in the volume of the transition state.[29] Although multiple factors may contribute, it is hypothesized that the reactions occurring within a water-induced, confined organic cage result in a high-pressure-like effect from the surrounding bulk water.[30] In addition, an enriched hydrogen bond donated by water at the interface is a key factor in facilitating this enhancement.[31] In particular, we discovered that the salting-out effect induced by high-concentration NaCl solutions suppressed micelle formation and increased the interfacial area, further enhancing the reaction efficiency. We hypothesized that this effect could provide a basis for the efficient functioning of MCFAs as Brønsted acid organocatalysts, particularly below their CMCs (Fig. 1B).

Herein, we report the "on-water" accelerated Brønsted acid-catalyzed aqueous reactions with MCFAs. As a representative model reaction, the allylboration of a general class of carbonyl compounds was demonstrated, exemplifying the scalability of the gram-scale synthesis. A crucial discovery in this study was the specific salting-out effect induced by NaCl, which proved to be essential for the success of the reaction. Remarkably, the reaction was also effectively catalyzed using very low-cost and unrefined additives such as seawater or edible sea salt, enabling the synthesis of high-purity pharmaceutical intermediates (APIs). The concentrated NaCl solution suppressed the self-assembly of MCFAs as surfactants, thereby enhancing the efficiency of the reaction under "on-water" conditions, specifically at the water–oil interface. This finding highlights the pivotal role of the salting-out effect in facilitating interfacial catalysis and offers a simple and sustainable approach for scalable and cost-effective organic transformations (Fig. 1C).

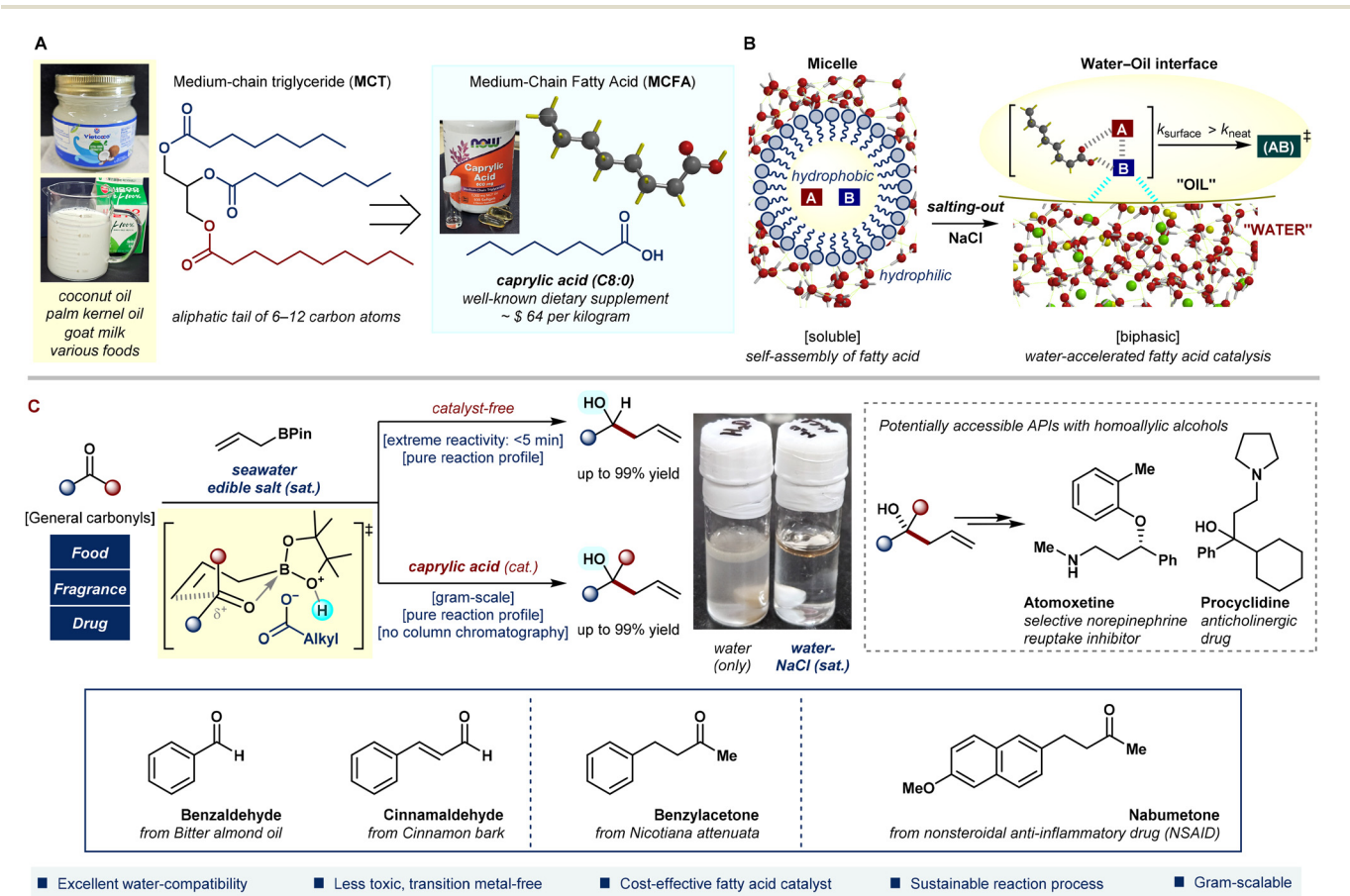


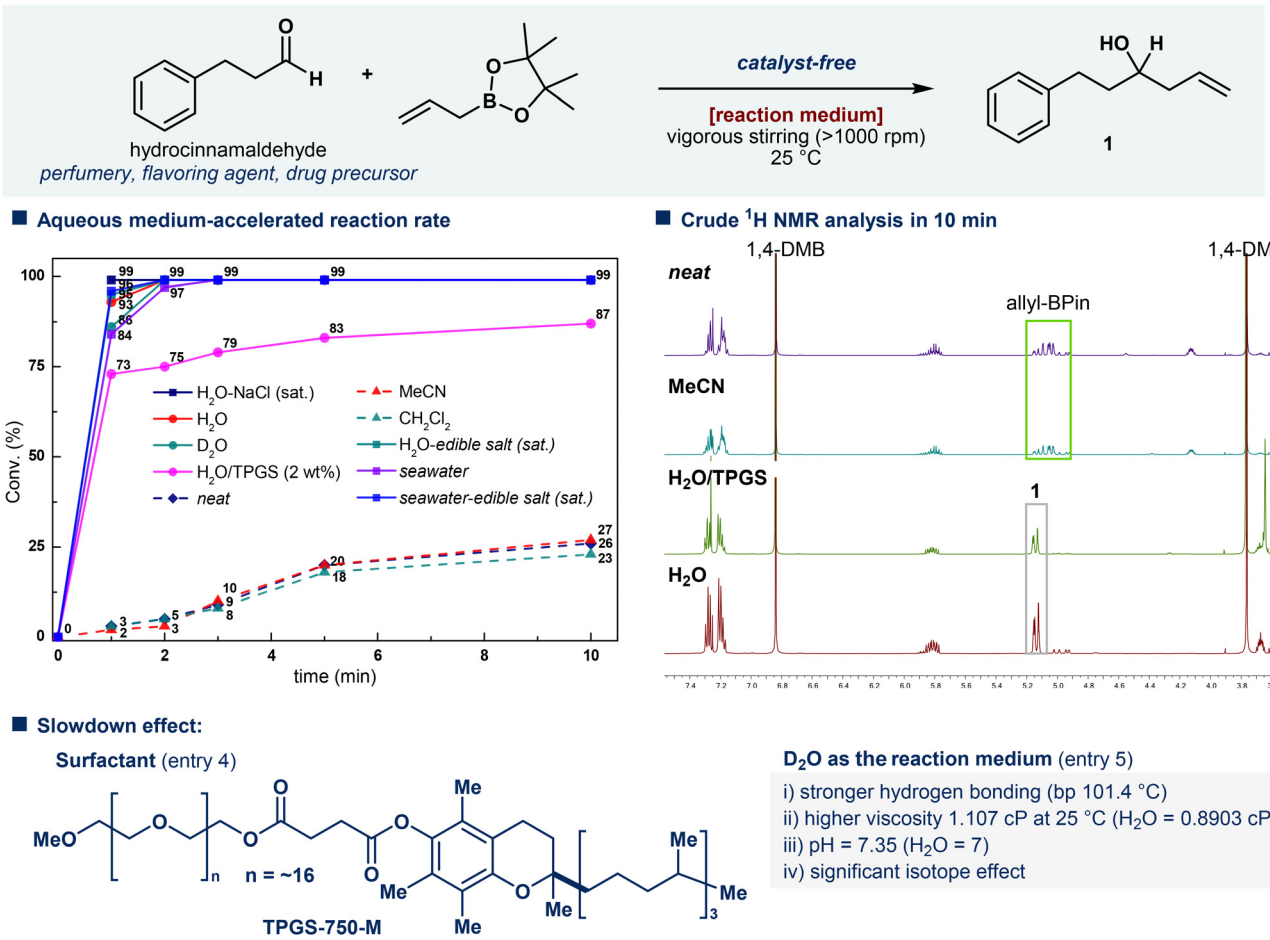
Fig. 1 Concept underlying this study. (A) Structure and properties of MCFAs. (B) Activated Brønsted acid catalysis under concentrated salty aqueous medium. (C) "On-seawater" accelerated aquacatalysis harnessing the remarkable salting-out effect.

Results and discussion

Condition optimization of catalyst-free allylation of aldehydes

We aimed to develop sustainable allylation reactions of general carbonyl compounds (Table 1). For our model reaction, we selected hydrocinnamaldehyde to initiate investigation with aliphatic aldehydes. Allylboronic acid pinacol ester was selected as the allylating reagent owing to its low toxicity and availability.[32] We first explored conventional organic solvents, such as dichloromethane and acetonitrile stirred at 25 °C. However, only very low conversions to product **1** were obtained (23% and 27% for entries 1 and 2, respectively). The neat condition (no solvent) gave a similarly low reactivity (26%, entry 3). Based on our previous findings, we speculate that aqueous conditions with bulk water as the reaction medium may improve the outcome. In particular, allylboronic acid pinacol ester is well known to exhibit reasonable activity in aqueous reaction systems.[33,34] To our surprise, "on-water" (water–oil

Table 1 Medium effect on the catalyst-free allylboration of aldehydes[a]



		Conv.[b] (%)				
Entry	[Reaction medium]	1 min	2 min	3 min	5 min	10 min
1	CH_2Cl_2	3	5	8	18	23
2	MeCN	2	3	10	20	27
3	*Neat*	3	5	9	20	26
4	TPGS-750-M (2 wt%)	73	75	79	83	87
5	D_2O	86	>99	>99	>99	>99
6	H_2O	93	>99	>99	>99	>99
7	**H_2O-NaCl (sat.)**	**>99**	**>99**	**>99**	**>99**	**>99**
8	H_2O-edible salt (sat.)	95	>99	>99	>99	>99
9	Seawater	84	>99	>99	>99	>99
10	**Seawater-edible salt (sat.)**	**96**	**>99**	**>99**	**>99**	**>99**

[a] Reactions were conducted using hydrocinnamaldehyde (0.1 mmol, 1.0 equiv.) and allyl-Bpin (0.12 mmol, 1.2 equiv.) in different reaction media (10 L mol^{-1}) at 25 °C. [b] Conv. (%) was determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard. min = minute.

biphasic) conditions were highly effective in this reaction. The use of pure water (10 L mol^{-1}, distilled) significantly improved the results, with >99% conversion in 10 min (entry 6).

Typical slowdown effects were observed under on-water conditions. Utilizing a designer surfactant developed by the Lipshutz group (TPGS-750-M, 2 wt% aqueous solution),[35] the entire system was emulsified, yielding a conversion of 87% within 10 min (entry 4). Although this outcome was slightly inferior to that achieved with pure water, the result aligned well with established on-water experimental observations.[26]

To investigate further, D_2O—a heavier and more viscous medium compared to H_2O—was employed. Similar to the results observed for H_2O, complete conversion was achieved within 10 min. However, the initial reaction rate was relatively slower (86% conversion in 1 min, entry 5) compared to the remarkable 93% conversion achieved within 1 min using H_2O. This notable difference can be attributed to the higher viscosity of D_2O, which likely reduces the effective interfacial surface area between the reactants and the aqueous medium by altering shear forces.[31] The reaction likely proceeds through acceleration at the water–oil interface, in line with the "on-water" theory introduced by Sharpless *et al.* and later supported theoretically by Jung and Marcus.[26,31]

Next, NaCl was used as a representative salting-out agent.[36] This approach yielded exceptional results, achieving >99% conversion within 1 minute (entry 7). These results align with the trends observed in other reported on-water reactions, highlighting accelerated reaction rates due to the effects of aqueous media.[26] Based on previous findings that hydrophobic agents enhance the efficiency of addition reactions, we replaced the reagent-grade NaCl (from a chemical supplier) with commercially available edible sea salt (from a grocery market). As a result, 95% conversion was achieved within 1 min, and 99% conversion was observed within 2 min (entry 8). While using bulk water represents an environmentally friendly approach to carbonyl allylation, achieving the initial goal of sustainable conditions and the reliance on distilled water present challenges. The need for repeated distillation in industrial-scale processes leads to an increased consumption of energy and resources.[37] From this perspective, seawater, which is one of the most abundant resources on the Earth, captured our attention. The utilization of seawater in chemical processes offers significant advantages in terms of cost, toxicity, and environmental impact.[38] Untreated seawater (salinity = 3.5%) sourced directly from Namhae (the southern sea of Korea, Pohang City) was used as the reaction medium (entry 9). The initial reactivity showed a slightly reduced conversion (84% in 1 min) compared to that achieved with distilled water. However, after 2 min, >99% conversion was achieved. We believed that the reactivity observed in seawater could be further enhanced by the addition of edible salt. Remarkably, the modification of this medium to saturated seawater (salinity = 26%) significantly improved the reaction rate, achieving 96% conversion within 1 min and complete conversion (>99% conversion) within 2 min (entry 10). These results highlight the potential for utilizing abundant and sustainable resources to develop sustainable and cost-effective synthetic processes.

Based on the optimized reaction conditions, a preliminary investigation of the substrate scope of aldehydes was conducted (Fig. 2). The reactions were carried out using seawater saturated with edible sea salt as the reaction medium, forming a water–oil biphasic interface. To ensure efficient mixing under these conditions, vigorous stirring (>1000 rpm) was performed.[29] Owing to the excellent reactivity of the system, all the reactions were completed within 5 min. The model substrate, hydrocinnamaldehyde, afforded product **1** in 99% isolated yield. To further investigate the reactivity of alkyl aldehydes, reactions were carried out with phenylacetaldehyde and 1-cyclohexenylaldehyde, affording products **2** and **3** in high yields of 95% and 90%, respectively. Cinnamaldehyde, a natural product readily obtained from cinnamon bark, afforded product **4** in 97% yield. Furthermore, the reactions with an aryl aldehyde proceeded smoothly, delivering product **5** in exceptionally high yield (99%). To further expand the substrate scope of aryl aldehydes incorporating electron-withdrawing and donating substituents, varying steric effects were investigated in our reaction system. *para*-Halogenated substrates (Cl and Br) afforded the corresponding products **6** and **7** in excellent yields (99%). Electron-withdrawing and donating substituents also provided desired products **8–10** in excellent yields (93%–99%). Biphenyl and 2-naphthyl incorporated bulky substrates afforded the desired products **11** and **12** in excellent yields (99%). Moreover, oxygen and sulphur-containing heteroaryl-aldehydes were highly active in the reaction, affording products **13** and **14** in 91% and 99% yields, respectively.

Condition optimization of catalytic allylation of ketones

We then continued to develop an efficient process for the allylation of less reactive ketones as acceptors[39] (Table 2). In particular, tetrasubstituted carbon centers in homoallylic alcohols have attracted our attention because of their potential as key intermediates in the synthesis of various active APIs.[40,41] Conventional methods such as the Hosomi–Sakurai allylation employing organosilicon reagents such as allyl trimethylsilane in moisture-sensitive metal Lewis acids have been widely investigated.[42,43] However, the application of anhydrous conditions to industrial processes poses significant challenges. The avoidance of organic solvents and metals in this catalytic system was expected to have a substantial impact.

Acetophenone, an aryl-alkyl ketone, was selected as the model substrate, and water was used as the reaction medium. Unlike aldehydes, ketones exhibited significantly lower reactivities under catalyst-free conditions, with negligible formation of product **15** (entry 1). At an elevated temperature of 60 °C, the reaction proceeded with 29% conversion after 24 h of stirring (entry 2). Consequently, we hypothesized that either Brønsted or Lewis acid catalysts would be required and proceeded to screen various candidates.

Inspired by our previous work on multicomponent aquacatalytic allylation, we preferably evaluated strong Brønsted

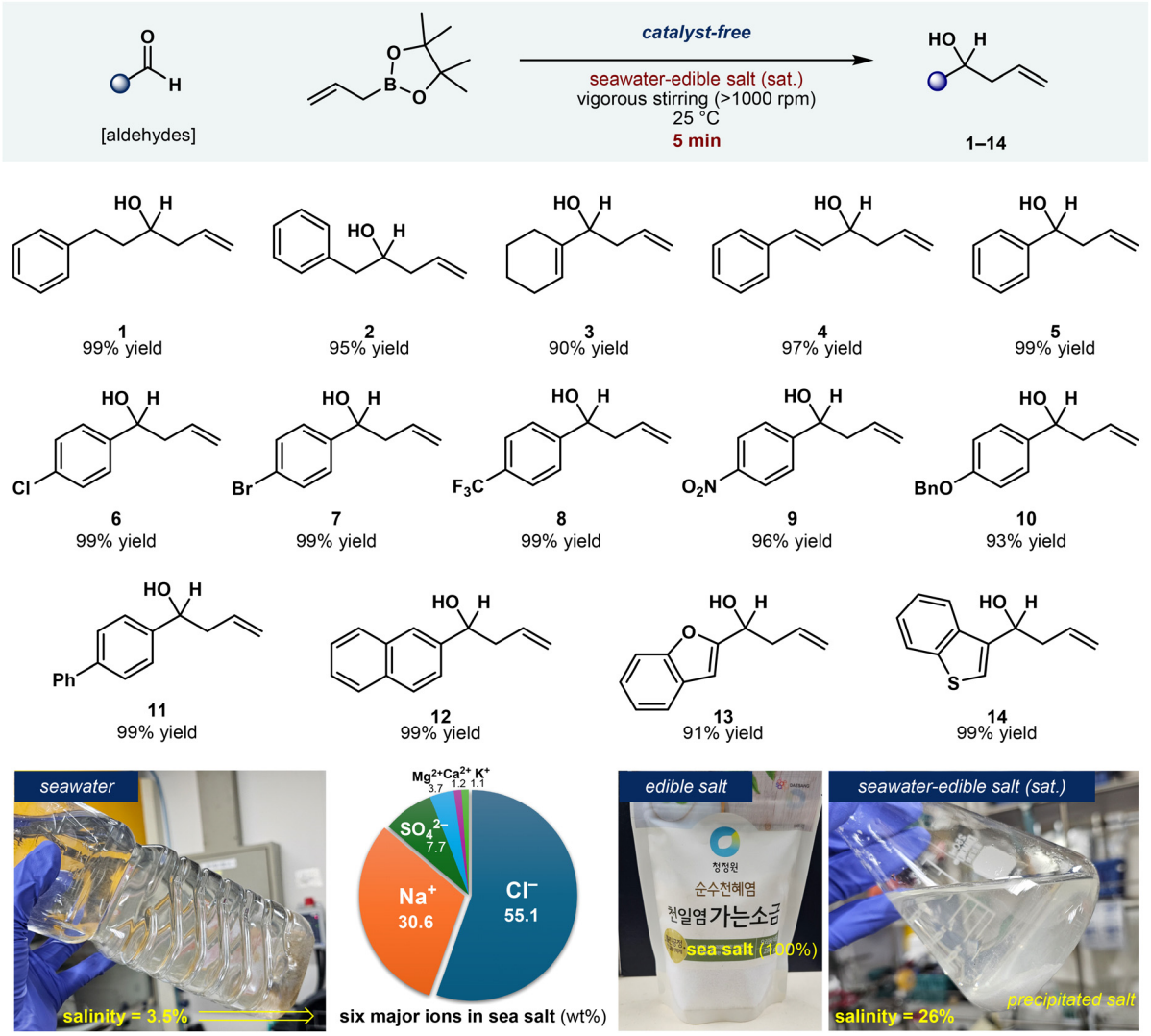


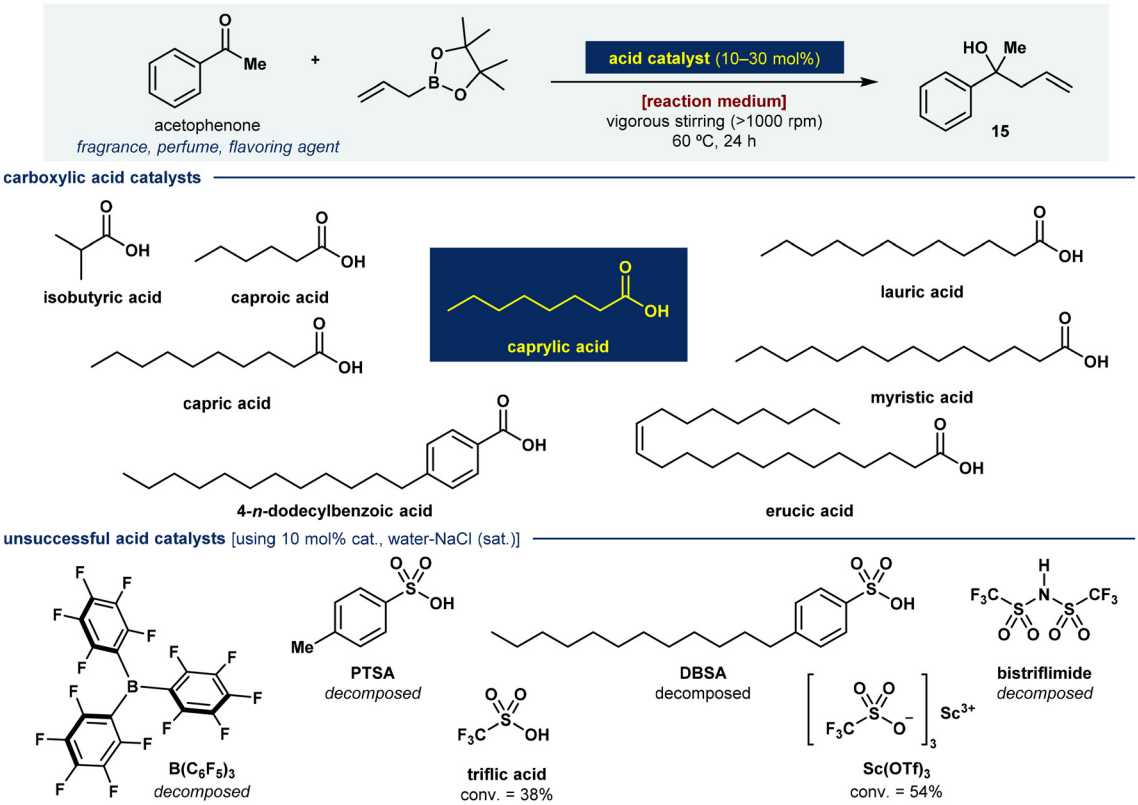
Fig. 2 Substrate diversity of the catalyst-free allylboration of aldehydes. Reactions were conducted using aldehyde (0.2 mmol, 1.0 equiv.), allyl-Bpin (0.24 mmol, 1.2 equiv.) and seawater-edible salt (sat.) at 25 °C for 5 min.

acids.[21] However, *p*-toluenesulfonic acid (PTSA), dodecylbenzenesulfonic acid (DBSA), and bistriflimide led to the complete decomposition of the substrate (~0%), whereas triflic acid (TfOH) showed limited catalytic activity (38% conversion). Among Lewis acids, tris(pentafluorophenyl)borane ($B(C_6F_5)_3$), a highly effective catalyst for Mukaiyama aldol reactions in water reported by the Loh group,[44] was inactive in this system. Scandium triflate ($Sc(OTf)_3$), commonly utilized by the Kobayashi group,[45] demonstrated marginally better activity but suboptimal performance, with a conversion of 54%. These findings highlight the need for novel and efficient catalysts.

Carboxylic acids are notable for their natural abundance, straightforward production, mild acidity, and low toxicity, all of which contribute to their safety and economic viability.[46] A diverse range of carboxylic acids was screened as catalysts (10 mol%). Simple highly water-soluble acids, such as formic acid (log P = −0.54) and acetic acid (log P = −0.26), exhibited no catalytic effect (31–33% conversion), while trifluoroacetic acid (log P = 1.35), benzoic acid (log P = 1.95), and *p*-dodecylbenzoic acid showed almost no reactivity (<1% conversion, entries 3–7). Considering the aqueous reaction medium, we hypothesized that introducing longer alkyl chains into the carboxylic acid structure might enhance the reactivity. Natural fatty acid screening revealed promising results. Caproic acid (C6:0, log P = 1.92), caprylic acid (C8:0, log P = 3.05), capric acid (C10:0, log P = 4.09) and lauric acid (C8:0, log P = 5.15), which are key components of MCTs,[3] significantly improved the conversion to 40%, 53%, 48% and 45% (entries 8–11). In contrast, longer-chain fatty acids such as myristic acid (C14:0, log P = 6.10) and erucic acid (C22:1, log P = 9.46), as well as branched acids such as isobutyric acid (log P = 0.45), showed no further improvement (entries 12–14).

Among the tested acids, caprylic acid emerged as the optimal catalyst owing to its lipophilicity (log P = 3.05). Temperature also played a critical role in the reaction. At 80 °C, the reactivity increased moderately, achieving 66% con-

Table 2 Condition optimization for catalytic allylation of ketones[a]



Entry	Carboxylic acid or salt (mol%)	Log *P* of acid	[reaction medium]	Conv. (%) of **5** [b]
1[c]	Without a catalyst	—	H_2O	5
2	Without a catalyst	—	H_2O	29
3	Formic acid (10)	−0.54 (−0.30)	H_2O	33
4	Acetic acid (10)	−0.26 (−0.09)	H_2O	31
5	Trifluoroacetic acid (10)	1.35 (0.21)	H_2O	<1
6	Benzoic acid (10)	1.95 (1.65)	H_2O	<1
7	4-*n*-Dodecylbenzoic acid (10)	(6.81)	H_2O	<1
8	Caproic acid (10)	1.92 (1.83)	H_2O	40
9	Caprylic acid (10)	3.05 (2.93)	H_2O	53
10	Capric acid (10)	4.09 (4.04)	H_2O	48
11	Lauric acid (10)	5.15 (4.60)	H_2O	45
12	Isobutyric acid (10)	0.94 (0.45)	H_2O	43
13	Myristic acid (10)	6.10 (4.97)	H_2O	32
14	Erucic acid (10)	9.46 (8.10)	H_2O	10
15[d]	Caprylic acid (10)	3.05 (2.93)	H_2O	66
16[e]	Caprylic acid (10)	3.05 (2.93)	H_2O	Trace
17[d]	Caprylic acid (10)	3.05 (2.93)	H_2O-NaCl (sat.)	79
18[d]	Caprylic acid (20)	3.05 (2.93)	H_2O-NaCl (sat.)	87
19[d]	Caprylic acid (30)	3.05 (2.93)	H_2O-NaCl (sat.)	92
20[f]	Caprylic acid (30)	3.05 (2.93)	H_2O	83
21[f]	Sodium caprylate (30)	—	H_2O-NaCl (sat.)	25
22[f]	**Caprylic acid (30)**	**3.05 (2.93)**	**H_2O-NaCl (sat.)**	**>99(99)**[g]

[a] Reactions were conducted using **7** (0.1 mmol, 1.0 equiv.), allyl-Bpin (0.3 mmol, 3.0 equiv.) and a carboxylic acid catalyst (10 mol%) in H_2O (10 L mol^{-1}) at 60 °C for 24 h. [b] Conv. (%) was determined by ^1H NMR analysis using 1,4-dimethoxybenzene as an internal standard. [c] At 25 °C. [d] At 80 °C. [e] At 100 °C. [f] Using allyl-Bpin (5.0 equiv.) at 80 °C. [g] Isolated yields are given in parentheses.

version (entry 15), while at 100 °C, the conversion decreased. This decrease was probably due to the increased solubility of the fatty acid above its CMC,[16] which disrupted the biphasic reaction environment for catalysis (entry 16). The salting-out effect of NaCl is particularly crucial in this system, as it further enhances the reactivity. Under optimized conditions, increasing the catalyst loading to 30 mol% led to complete conversion to the desired product **15** (entries 17–20, and 22). The reaction yield dropped dramatically to 25% when sodium caprylate was used (entry 20).

Substrate scope of allylation of ketones

Based on the optimized reaction conditions, the substrate scope for the allylation of various ketones was explored (Fig. 3). Ketones substituted with alkyl–alkyl groups are generally less reactive as acceptors, presenting a significant challenge. However, under our salting-out-enhanced "on-water" conditions, they were successfully converted to compounds **16** and **17** in excellent yields (97% and 91%, respectively). The method was further extended to cyclic ketones, yielding products **18** and **19** with remarkable efficiencies (up to 95% yield). Similarly, alkenyl and alkynyl ketones underwent quantitative transformations into the expected products, **20** and **21**, in 99% and 96% yields, respectively. Substrates bearing (thio)ester functional groups, such as β-ketoesters and α-ketothioesters, also exhibited excellent functional group tolerance, yielding compounds **23** and **24** in 97% and 90% yields, respectively. A wide range of (hetero)aryl-alkyl ketones were also converted to the desired products without complications in very high yields (compounds **15–38**, up to 99%). Additionally, gram-scale reactions with ketone substrates were successfully conducted, maintaining excellent efficiency (99% yield for compounds **15** and **34**).

We further demonstrated the utility of this method by performing late-stage modifications on ketone-containing natural products and pharmaceuticals. Nabumetone,[47] a nonsteroidal anti-inflammatory drug (NSAID), and flavone,[48] a compound commonly found in plant-derived foods, were efficiently transformed into the desired products in high yields (99% yield for compound **39**; 98% yield with anti/syn = 3.7/1 for compound **40**). This investigation highlights the broad applicability and robustness of the developed aqueous allylation protocol, even with challenging substrates and late-stage functionalization.

Development of chromatography-free purification methods and synthetic applications

To achieve an efficient and sustainable purification process, it is necessary to develop a purification protocol that does not require column chromatography. A 1.0 gram scale synthesis of benzylacetone was conducted to isolate the product solely through extraction. The reaction was performed using untreated seawater saturated with edible sea salt as a medium (Fig. 4A). Upon completion of the reaction, the crude mixture was subjected to extraction-based purification. The most challenging aspect of the purification process was the removal of the residual allyl-Bpin and caprylic acid. Previous studies have indicated that pinacol boronate esters undergo hydrolysis under acidic conditions.[49] Subsequently, 6 N HCl (aq.) was added to the crude mixture, which was then stirred for 24 h. This treatment transformed the pale-yellow crude mixture into a dark red solution, and the resulting unreacted components were simply removed through extraction. Next, the removal of residual caprylic acid, which was used as the catalyst, was investigated. The water solubility of caprylic acid increases with temperature,[50] allowing its efficient removal through hot water extraction (see the ESI†). To validate the efficacy of this protocol, gas chromatography (GC) was performed on both crude and purified products. The residual allyl-Bpin, caprylic acid, and minor benzylacetone impurities were removed entirely, yielding a highly pure (>99%) GC trace of product **16**. In the case of the aldehyde, the product **1** was also successfully obtained through our chromatography-free protocol (see the ESI†), highlighting its potential for simplifying sustainable and economical processes.

To further demonstrate the utility of these reaction products, olefin metathesis was performed using **15** (Fig. 4B). Using the Grubbs-II catalyst, compound **15** was successfully converted to compound **41** with 80% yield. This excellent functional group tolerance underscores the potential of this method for API synthesis.

The compatibility of our catalytic allylation system with water and its transition-metal-free nature suggest that it is particularly practical for biomolecule functionalization applications.[51] In this context, the reaction system aligns closely with the biomimetic conditions required for constructing DNA-encoded libraries (DELs), a powerful tool in drug discovery.[52] Notably, the allylation of ketones tethered to DNA has not yet been reported, making this a significant opportunity for advancing its biochemical applications. To extend the applicability of this reaction, we investigated its use in on-DNA allylation (Fig. 4C). First, amide coupling was performed by reacting a headpiece-modified DNA molecule[53] with 4-acetylbenzoic acid, hexafluorophosphate azabenzotriazole tetramethyl uranium (HATU), *N*,*N*-diisopropylethylamine (DIPEA), and pH 9.5 borate buffer at 80 °C for 24 h. Compound **42** was characterized using HPLC and UPLC, achieving a conversion of 92% (HRMS: *m*/*z* calcd $[M - H]^-$ = 5327.0540; found $[M - H]^-$ = 5327.1348). Compound **42** was diluted with double-distilled H_2O. Allyl-Bpin (500 equiv.) and caprylic acid (100 equiv.) were added, and the reaction was performed at 80 °C for 24 h. The desired product **43** was successfully obtained with 56% conversion, as confirmed by HPLC and UPLC (MS: *m*/*z* calcd $[M - H]^-$ = 5369.1010; found $[M - H]^-$ = 5369.1750). This study highlights the utility of the developed catalytic system for sustainable and efficient aquatic allylation processes and its broad applicability to advanced biochemical transformations such as DNA-encoded library synthesis.

Mechanistic investigation

Investigating the water-promoted rate acceleration in biphasic reactions involving a catalyst is inherently more complex than that under catalyst-free conditions. The mechanism underlying this enhancement was well categorized by Kobayashi and Kitanosono,[54,55] who classified on-water reactions involving catalysts as type III. In our system, elevated temperatures increase the solubility of caprylic acid in water; however, the salting-out effect induced by saturated Na^+ and Cl^- ions may be expected to suppress micelle formation (illustrated in Fig. 1C). It is hypothesized that the reaction predominantly occurs at the interface between the oil phase (the ketone, allyl boronate, and caprylic acid (log *P* = 3.05)) and the ion-saturated aqueous phase. Jung and Marcus proposed that the free –OH groups in bulk water form stronger hydrogen bonds with hydrogen-bond acceptors in the transition state.[31]

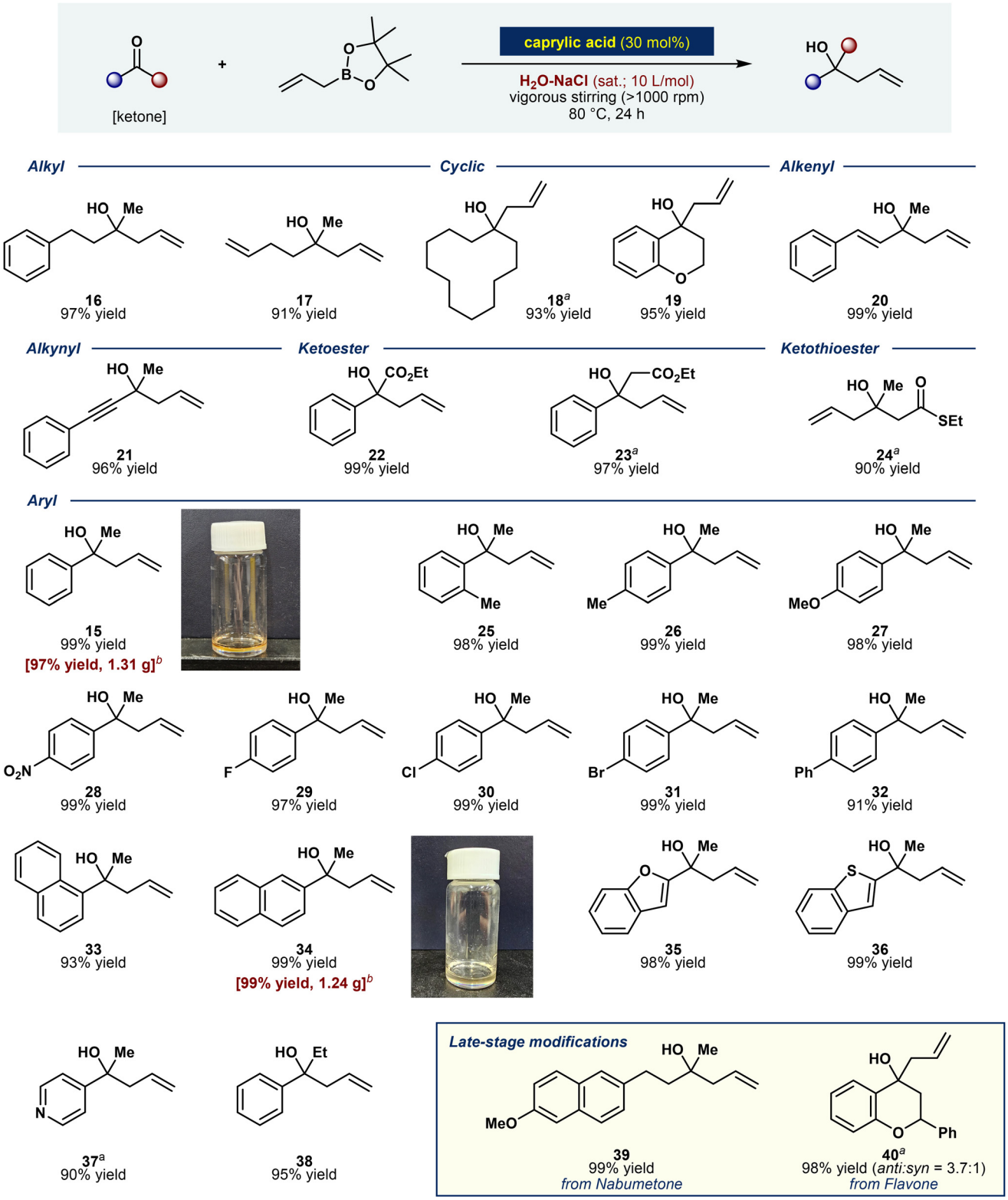


Fig. 3 Substrate scope of the fatty acid-catalyzed allylboration of ketones. Reactions were conducted using ketone (0.2 mmol, 1.0 equiv.), allyl-Bpin (1.0 mmol, 5.0 equiv.), caprylic acid (30 mol%), and H_2O-NaCl (sat., 2.0 mL) at 80 °C for 24 h. [a] 48 h of reaction time. [b] Isolated yield of gram-scale synthesis.

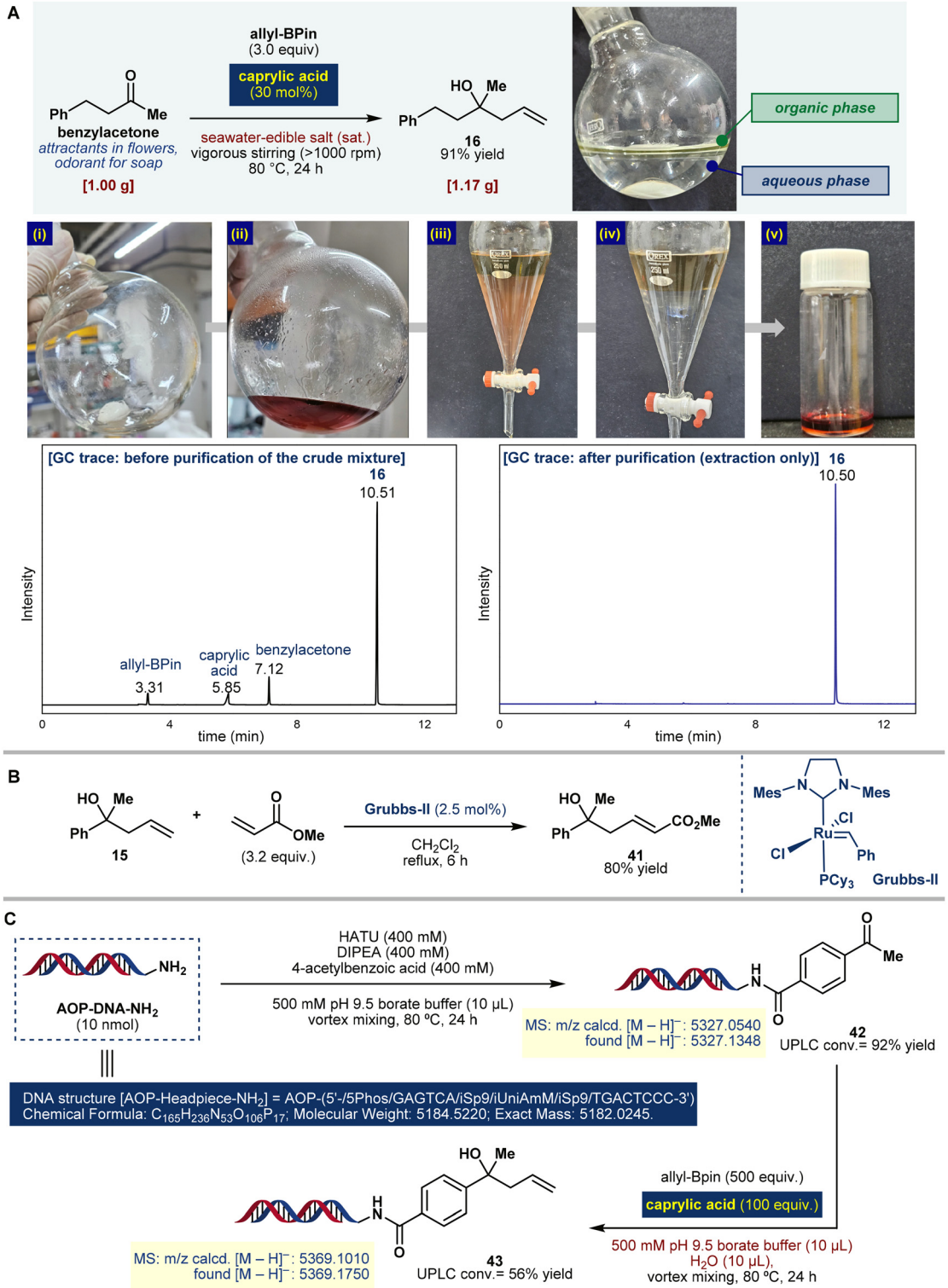
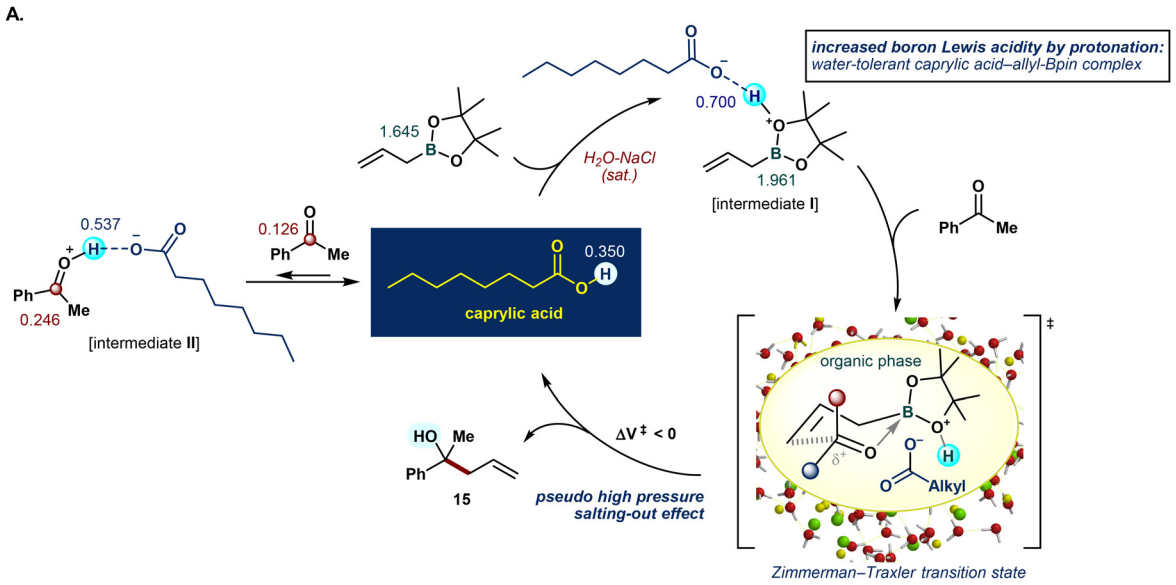
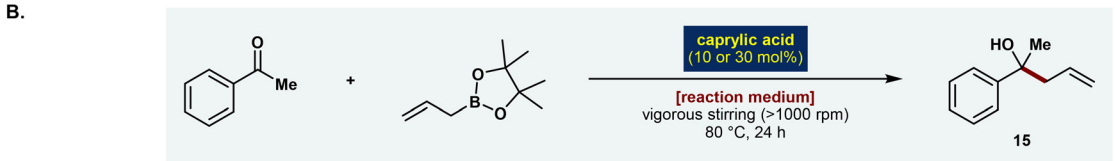
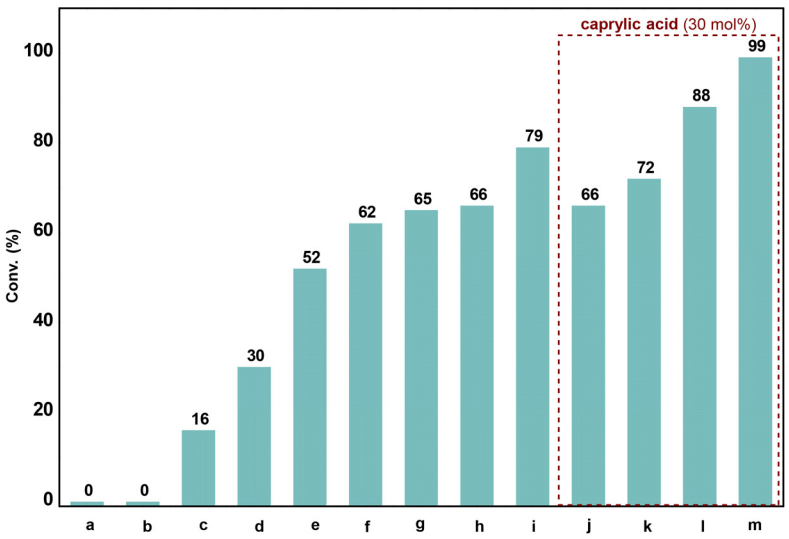


Fig. 4 Synthetic utilities. (A) Reaction conducted using benzylacetone (1.0 g), allyl-Bpin (3.0 equiv.), caprylic acid (30 mol%), and seawater-edible salt (sat.) at 80 °C for 24 h. Description of pictures: (i) concentrated crude mixture after reaction completion. (ii) Addition of 6 N HCl (aq.). (iii) Extraction with ethyl acetate/water to remove organic impurities. (iv) Extraction with ethyl acetate/hot water to remove the remaining caprylic acid catalyst. (v) Obtained desired product **16** (>99% GC purity). (B) Derivatization: catalytic olefin metathesis of the product. (C) On-DNA bioconjugation process.





Entry	[reaction medium]
a	acetone
b	CH_2Cl_2
c	MeOH
d	H_2O-$LiClO_4$ (sat.)
e	H_2O/TPGS (2 wt%)
f	*neat*
g	D_2O
h	H_2O
i	H_2O-NaCl (sat.)
j	H_2O-NaCl (sat.) / PhMe (5.0 equiv.)
k	H_2O-NaCl (sat.) / PhMe (3.0 equiv.)
l	H_2O-NaCl (sat.) / PhMe (1.0 equiv.)
m	H_2O-NaCl (sat.)



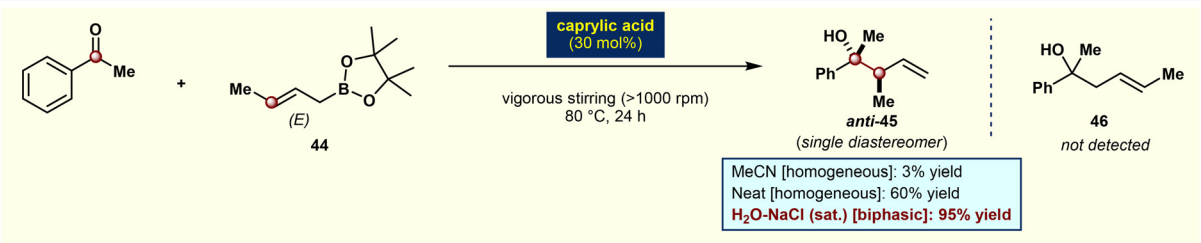


Fig. 5 Mechanistic investigation. (A) Proposed catalytic cycle and DFT-calculated Mulliken charges of selected atoms. (B) Effect of the reaction medium on the catalytic allylboration of acetophenone. Reactions were conducted using acetophenone (0.1 mmol, 1.0 equiv.), allyl-Bpin (0.3 mmol, 3.0 equiv.), caprylic acid (10 or 30 mol%), and the reaction medium at 80 °C for 24 h. Conv. (%) was determined by ^{1}H NMR analysis using 1,4-dimethoxybenzene as an internal standard. (C) Validation of the Zimmerman–Traxler mediated mechanism. The reaction was conducted using acetophenone (0.1 mmol, 1.0 equiv.), compound **44** (0.5 mmol, 5.0 equiv.), caprylic acid (30 mol%), and H_2O-NaCl (sat.) at 80 °C for 24 h.

Additionally, based on computational studies, Roke *et al.* reported that the surface of pure water is more acidic than the bulk,[56] suggesting that the acidity of hydrated caprylic acid is enhanced at the oil–water interface. This increased acidity may facilitate strong hydrogen bonding interactions with hydrogen bonding acceptors such as the oxygen atom adjacent to the boron atom in allyl-Bpin.[57,58] To further elucidate this phenomenon, density functional theory (DFT) calculations were performed (Fig. 5A). A key aspect of this investigation was to determine whether the catalytic activity of caprylic acid could be attributed to its –COOH group, which activates allyl-Bpin to provide the [intermediate-**I**]. DFT calculations revealed that the Mulliken charge of the boron atom in allyl-Bpin increased from 1.645 in the absence of a catalyst to 1.961 in the presence of caprylic acid. This suggests that caprylic acid forms a hydrogen-bonded complex with allyl-Bpin, enhancing its Lewis acidity and generating additional reactive organoboron intermediates. For comparison, further calculations were performed to examine the interaction between caprylic acid and the carbonyl oxygen of acetophenone ([intermediate-**II**]). As a result, the Mulliken charge on the carbonyl carbon of acetophenone increased from 0.126 to 0.246 upon interaction with caprylic acid. This outcome suggests that caprylic acid preferentially interacts with the oxygen atom in allyl-Bpin rather than with the carbonyl oxygen in acetophenone (see the ESI† for details).[58]

To validate whether the reactive intermediate benefited from the on-water effect, the reactivities of various reaction media were compared (Fig. 5B). Reactions were conducted with 10 mol% caprylic acid at an optimized temperature of 80 °C. Bulk water yielded 66% conversion (entry h), whereas organic solvents such as acetone and dichloromethane were completely inactive. Methanol exhibited a limited reactivity (16% conversion; entries a–c). Although the initial rate was slightly slower, D_2O gave a result comparable to that of H_2O (entry g). The designer surfactant H_2O/TPGS (2 wt%) resulted in only 30% yield (entry d), while neat conditions improved the yield to 62% (entry f). These findings indicate that homogeneous reaction systems are unsuitable, with their reaction performance closely linked to the substrate concentration; higher concentrations under neat conditions enhance the reaction. The superior reactivity observed in bulk water is likely derived from the biphasic system, which creates a confined organic cage that exerts a high-pressure-like effect on the reactants.[30] This confinement compresses the reactive organic phase, leading to a negative activation volume ($\Delta V^{\ddagger} < 0$), which is known to accelerate transformations, particularly those involving addition-type reaction mechanisms.[29] This hypothesis is consistent with the observed trends: a hydrophobic agent[34] like NaCl enhances conversion to 79% (entry e), while an anti-hydrophobic agent[59] like $LiClO_4$ reduces it to 52% (entry d). Furthermore, increasing the catalyst loading significantly improves the reactivity, highlighting the critical role of the catalyst (entries j–m).

To ensure that the catalytic system followed a Zimmerman–Traxler-type transition state,[60] we replaced allyl-Bpin with *trans*-crotylboronic acid pinacol ester (compound **44**, Fig. 5C). The reaction yielded only compound **45**, with a methyl group at the α-position in 95% yield. Notably, a single diastereomer with an *anti*-configuration was observed, indicating that the nucleophilic attack on the carbonyl carbon occurred exclusively at the terminal sp^2-carbon atom. In accordance with our expectations, reactions conducted in organic solvents (MeCN) afforded less than 5% yield, and even under solvent-free conditions, the yield was low (60%). These results support the involvement of the Zimmerman–Traxler transition state.

Conclusions

In summary, we have developed a sustainable aqueous catalytic approach for carbonyl allylation, leveraging unrefined seawater and sea salt to harness the salting-out effect. This method achieved (i) efficient, catalyst-free allylation of aldehydes and (ii) caprylic acid-catalyzed allylation of ketones using a cost-effective, nontoxic fatty acid commonly employed in the food industry, with bulk water as the reaction medium. The process demonstrated scalability, enabling gram-scale synthesis with chromatography-free purification and offering a promising pathway for cost-efficient API production. Additionally, the mild reaction conditions and water compatibility facilitate on-DNA conjugation, potentially transforming the development of DELs, a critical innovation in drug discovery. We believe that this study provides a robust foundation for further advancements in environmentally friendly, water-compatible, and fundamental catalytic systems for challenging applications.

Data availability

The data supporting the findings of this study are available within the article and its ESI.† Additional data are available from the corresponding author upon request.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The generous support from the Ministry of Science, ICT, and Future Planning of Korea (RS-2023-00259659 and RS-2023-00219859) and the Ministry of Education (2022R1A6C101A751 and 2022R1A6C102A913) is gratefully acknowledged.

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