Synthetic Organic "Aquachemistry" that Relies on Neither Cosolvents nor Surfactants

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ABSTRACT: There is a growing awareness of the underlying power of catalytic reactions in water that is not limited to innate sustainability alone. Some Type III reactions are catalytically accelerated without dissolution of reactants and are occasionally highly selective, as shown by comparison with the corresponding reactions run in organic solvents or under solvent-free conditions. Such catalysts are highly diversified, including hydrophilic, lipophilic, and even solid catalysts. In this Outlook, we highlight the impressive characteristics of illustrative catalysis that is exerted despite the immiscibility of the substrates and reveal the intrinsic benefits of these enigmatic reactions for synthetic organic chemistry, albeit with many details remaining unclear. We hope that this brief introduction to the expanding field of synthetic organic "aquachemistry" will inspire organic chemists to use the platform to invent new transformations.
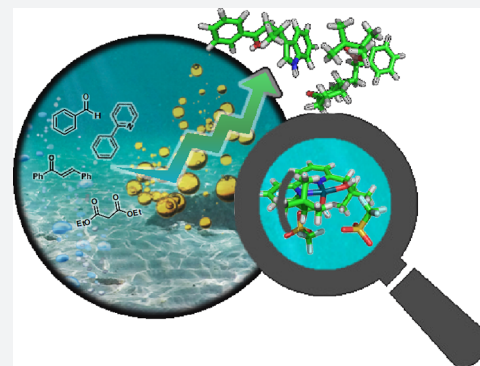
INTRODUCTION

Modern synthetic organic chemistry relies heavily on the use of vast amounts of organic solvents to perform many aspects of both laboratory synthesis and industrial production. Solvents are used to mediate heat dissipation and to bring the reactants together in a uniform phase to enhance the rate of those chemical reactions that are governed by the collision frequency between reactants. This implicit view that the reactants should be dissolved, however, perpetuates a belief that a chemical reaction does not take place unless the reactants are in solution, a view that can be traced back to a quote ascribed to Aristotle.[1] In recent years, growing concerns over the environmental impact resulting from the accumulated use of solvents in chemical production have driven the streamlining of synthetic methodologies in line with the principle of green sustainability. Driven in part by these external stimuli, the use of water as a reaction medium without the aid of organic cosolvents has emerged as a preferred remedy[2] in addition to solvent-free mechanochemical techniques that have recently seen a resurgent,[3] albeit seldom adopted, approach in organic synthesis. Both approaches, although old-fashioned, transcend the traditional paradigm of "solution chemistry" and obviate the need for bulk dissolution of reactants. The fledgling field of organic chemistry was intimately bound up with the use of water as a reaction medium; venerable examples include Wöhler's urea synthesis in 1828,[4] self-condensation of acetone in 1838,[5] Kolbe electrolysis in 1847,[6] and even Robinson's landmark synthesis of tropinone in 1917.[7] The historical links between organic chemistry and aqueous environments, however, lapsed into obscurity, largely in the context of

flourishing organometallic chemistry that typically forces us to operate in rigorously anhydrous environments. Not until the rediscovery of rate acceleration in water by Breslow,[8] subsequently termed the "on-water" effect,[9] did organic chemists dare to again manipulate chemical reactions in the presence of water. Even today, the apodictic benefits of embracing sustainability notwithstanding, organic chemists are generally reluctant to harness water as a reaction medium.

A common approach that is used to sidestep an immiscibility issue is appending surfactants to partition lipophilic organic compounds. It was reported that the amount of organic waste that is produced can be reduced tremendously by the use of 10^{-2} to 10^{-4} M surfactant solutions instead of 100% organic solvents.[10] Extensive efforts to realize the maximum effect of surfactants even under dilute conditions (especially catalytic amounts) resulted in the advent of designed nonionic surfactants[11] and surfactant-combined catalysts such as metal dodecylsulfates[12] or amphiphilic ligands.[13] In parallel, the use of dilute solutions of these surfactants has enabled multifarious catalytic reactions including asymmetric synthesis to be performed without the assistance of organic solvents.

Apart from surfactant-based approaches, surfactant-free catalytic reactions in water, "aquachemistry", have come to

be recognized as an offbeat yet useful tool in synthetic organic chemistry. One may perceive this as a biomimetic regime because water is a peerless medium in which nature furnishes complex molecules. The biosynthetic process is critically dependent on water: it regulates reaction kinetics, selectivity, substrate binding, and conformation. In addition, *in vivo* reactions are often not reproducible based on conventional organic chemistry that has been developed in organic solvents, which does encourage us to explore this straightforward, albeit counterintuitive, approach. For example, the reactants of *in vivo* reactions are not necessarily water-soluble, for example, 25-hydroxylation of practically water-insoluble[14] cholecalciferol (vitamin D3) in human liver (Scheme 1) and enzymatic cellulose hydrolysis.

Scheme 1. Example of an Enzymatic Reaction of a Water-Insoluble Compound

Cholecalciferol (vitamin D3)
solubility: 34 pM
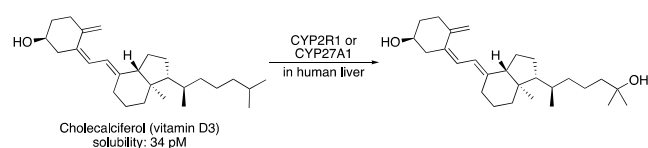
For all that, one may be bewildered by the absence of reliable methods to leverage this counterintuitive chemistry in organic synthesis, especially when one would like to transform water-immiscible reactants. To stimulate discussions, such surfactant-free catalytic reactions using water as a reaction medium can be roughly classified into three types (Figure 1).[15]
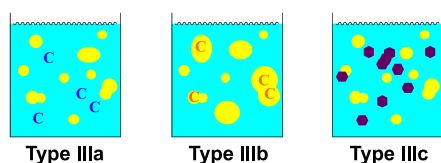

Figure 1. Schematic images of Type III reactions with catalysts (no cosolvents, no amphiphilic molecules). Yellow shapes represent droplets consisting of reactant(s); capital C indicates a soluble catalyst (blue: soluble in water, red: lipophilic and soluble in suspended droplets), and purple hexagons indicate an insoluble solid catalyst.

The physicochemical properties of catalysts determine whether they are Type IIIa, IIIb, or IIIc, pushing aside supramolecular catalysts such as enzymes, abzymes, capsules, cyclodextrins, and hydrogels. Type IIIa reactions involve water-soluble catalysts, IIIb reactions involve lipophilic catalysts that are miscible with reactants, and IIIc reactions correspond to reactions in which neither reactants nor catalysts are water-soluble and are immiscible with each other. Above all, Type IIIc reactions are highly counterintuitive, and it is difficult to anticipate positive outcomes because the reactions take place where neither reactants nor catalysts are miscible with water.

One feasible advantage of this chemistry is rate acceleration as is often the case with catalyst-free reactions. Although catalysts often alter the mechanism of reactions in substantial ways, the catalytic activation of reactants is compatible with accelerative effects at the surface of the water droplets. Moreover, Type IIIa−c reactions sometimes allow unusual selectivity that differs from that in organic solvents. In this context, asymmetric synthesis without the use of cosolvents or surfactants is particularly challenging because the precise and

> Apart from surfactant-based approaches, surfactant-free catalytic reactions in water, "aquachemistry", have come to be recognized as an offbeat yet useful tool in synthetic organic chemistry.

subtle interactions essential for stereodifferentiation may be disrupted by water acting as both a hydrogen-bond donor and acceptor; existing methods that address these issues are thus still few. An early form of a catalytic asymmetric Type III reaction emerged in the early 2000s[16,17] with a catalyst that was likely dissolved in suspended droplets (Type IIIb).[18] Although Type IIIb reactions catalyzed by proline derivatives were subsequently reported in 2006,[19] these examples are not regarded as following the "on-water" mechanism.[15] This is because the effect of water is concluded to be the suppression of the formation of key intermediates within the cycle as well as oxazolidinones,[20] as is often quoted in various discussions.[21]

Type III reactions may be characterized by an expedient isolation of organic compounds pursuant to green and sustainable chemistry. The postreaction mixtures can separate into two or three phases, thereby avoiding the need for extractive workup. In particular, Type IIIc reactions are ideal because centrifugation of the postreaction mixtures would allow their separation into water, an organic phase including products, and a solid catalyst (*vide infra*). On the other hand, one may be concerned that the innate heterogeneity of Type III reactions is a deterrent for applications at manufacture scale. Although there has been indeed no application to an industrial process, Novaltis's adoption of a catalyst-free "on-water" process en route to the anticonvulsant rufinamide[22] and many successes of gram-scale Type III reactions using catalysts including unreported results will lower the barrier for process chemists to embrace "aquachemical" approaches. In addition, many chemical mixing tools including the venturi tube, ball miller, and microfluidic devices may help drive future success. When scaled up, "aquachemical" exothermic processes become safer and more selective because of an excellent heat capacity of water.

We herein discuss illustrative examples to showcase their intrinsic values in synthetic organic chemistry that complement techniques using organic solvents. We also summarize the challenges involved in better understanding the seemingly capricious catalysis that is not exerted in analogous homogeneous reactions performed in organic solvents.

■ VIGNETTES OF SYNTHETIC ORGANIC "AQUACHEMISTRY"

It is important that both reactants and catalyst are embedded in the surface of the water droplets for efficient Type III reactions. The involvement of interfacial water molecules in the reaction mechanism is anticipated to underlie the water-induced enhancement of the reactivity and to determine selectivity control.[23] Indeed, the pronounced role of interfacial water molecules is often seen in enzymatic catalysis.

■ HYDROGEN-BONDING AND WATER-INDUCED HYDROPHOBIC AMPLIFICATION

The water-mediated hydrogen-bonding network is found in thymidylate synthase to reduce the energy necessary to reach the intermediate.[24] Syrén and co-workers adopted an enzyme engineering strategy for accelerated catalysis in which water bridges between the productive transition state and the protein backbone were redesigned to stabilize the transition state.[25] Although noncovalent hydrogen-bond organocatalysis is *a priori* not amenable to Type III reactions, a noteworthy example of epoxide hydrolases that detoxify living cells by epoxide hydration supports the viability of this catalysis. In the transition-state model, two tyrosine residues act through hydrogen bonds to activate the epoxide, with a water molecule activated by the nearby histidine and aspartic acid residues. The role of the two tyrosine residues was confirmed using the double mutant, which showed no detectable catalytic activity, and by inhibition studies with ureas.[26]

> Type III reactions may be characterized by an expedient isolation of organic compounds pursuant to green and sustainable chemistry.

The concept of highly enantioselective noncovalent organo-catalysis was reported by Song and co-workers (Table 1),[27]

Table 1. Water-Accelerated Type IIIb Noncovalent Hydrogen-Bond Catalysis
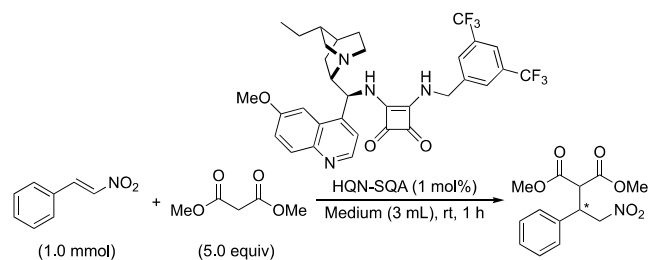
entry	medium	conv (%)[a]
1	brine	>99 (92)[b]
2	LiClO4 in H2O (sat.)	14
3	MeOH	34
4	CH2Cl2	52
5	THF	21
6	toluene	17
7	CH3CN, 1,4-dioxane	<10

[a]Calculated based on crude ^{1}H NMR analysis. [b]Enantiomeric excess (% ee).

wherein the use of brine provided a remarkable rate acceleration over organic solvents while retaining high levels of enantioselectivity. A significant decline in the level of conversion in saturated LiClO4 solution is the same observation as catalyst-free Type III reactions.[28] Therefore, the authors attribute the beneficial role of water to the hydrophobic hydration effect. The benefits of adopting "aquachemistry" are evidenced by the successful 1,4-addition of dithiomalonate with less reactive β,β-disubstituted nitro-alkenes with no conversion in organic solvents.[29] Notably,

these Type IIIb protocols are amenable to multigram-scale synthesis, and the catalyst can be quantitatively recovered as a solid by filtration from postreaction mixtures after addition of methylcyclohexane.[27]

■ [Cp*MCl2]2-CATALYZED C(sp²)−H BOND ACTIVATION

The contribution of water to C(sp²)−H bond activation with the assistance of carboxylates has been underpinned by several Type III metal-catalyzed cross-coupling reactions,[30] in which water facilitates the production of both coordinatively unsaturated metal species and a water-bound metal species.[31] The involvement of interfacial water molecules in a concerted metalation−deprotonation (CMD) mechanism was proposed for a rhodium-catalyzed Type IIIb reaction (Table 2).[32] The

Table 2. Water-Involved Type IIIb Rhodacycle Formation/ N-Boc Amidation in Water

entry	medium	conv (%)[a]
1	H2O	88
2	DCE, PhMe, CH3CN, THF, DMSO, ^{i}PrOH	<5
3	hexane	8
4	DMF	11
5	DCE/H2O (0.2, 1.0, or 10 equiv)	<5
6	^{i}PrOH/H2O (10 equiv)	8
7	−(neat)	25 (16 h)
8[b]	H2O	83
9[b]	DCE	46 (48)[c]

[a]Calculated based on crude ^{1}H NMR analysis. [b]Rhodacycle **A** was used instead of [Cp*RhCl2]2 as a catalyst. [c]For 12 h.
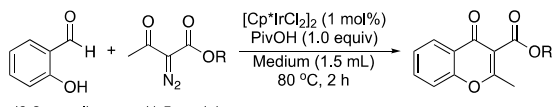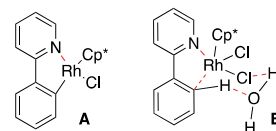

authors confirmed that a quantitative amount of rhodacycle **A** was formed when [Cp*RhCl2]2 was mixed with 2-phenyl-pyridine in water at an elevated temperature and that the rhodacycle **A** was able to catalyze the reaction (entry 8) as the active species. Given that general rhodacycle formation via C−H activation commences with the cleavage of dimeric [Cp*RhCl2]2 to form a reactive monomeric [Cp*RhCl(OAc)] in the presence of NaOAc,[33] it is considered that water substitutes for the acetate ion. The negative results observed in the presence of catalytic amounts of water under homogeneous conditions (entries 5 and 6) strongly suggest the involvement of interfacial water molecules, as depicted in transition state **B**. Less than 50% conversion even with a longer reaction time in DCE (entry 9) suggests that half the amount of 2-phenylpyridine may act as a base. Within the catalytic cycles, rhodacycle **A** can undergo hydration to form an aqua complex or monohydroxide, leading to a water-promoted mechanism involving intermolecular hydrogen bonding.

Rare water-accelerated iridium(III) catalysis for aldehyde C−H activation with the assistance of carboxylic acid was

reported. The annulation between salicylaldehyde and α-diazoester proceeded efficiently in water, allowing access to chromane synthesis (Table 3).[34] Incubation of the catalyst

Table 3. Water-Promoted Type IIIb Annulation of Salicylaldehyde with α-Diazo Carbonyl Compound

(0.2 mmol)   (1.5 equiv)

entry	R	medium	yield (%)
1	Et	H_2O	90 (75)[a]
2	Et	MeOH	(68)[a]
3	Et	CHCl$_3$	(40)[a]
4	Et	DCE	(70)[a]
5	Et	TCE	(55)[a]
6[b]	^{t}Bu	H_2O	86[c]
7[b]	^{t}Bu	DCE	53

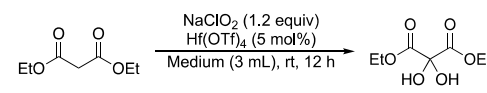[a]AcOH was added instead of PivOH. [b]100 °C, 8 h. [c]A chromanone was obtained.
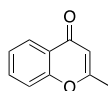
with salicylaldehyde in D_2O resulted in around 17% deuterium exchange, indicating the reversibility of aldehyde C−H activation. The use of a *tert*-butyl diazoester resulted in a product switch induced by water and led to one-pot annulation−decarboxylation (entries 6 and 7). The reaction can be carried out on a gram scale.

■ METAL-BOUND WATER MOLECULES

Metal-bound water molecules form much stronger hydrogen bonds than bulk water molecules,[35] thereby participating in intramolecular hydrogen bonds within the first hydration shell[36] and sometimes conferring a pronounced Brønsted acidity[37] that governs the aqua-hydroxo equilibrium. The resulting hydroxo metal complexes are expected to be promising Lewis acid/Brønsted base hybrid catalysts for bond-forming reactions. Because they have been infrequently found in catalyst structures, their catalytic versatility may have been overlooked in organic synthesis. Considering that calculations revealed that the surrounding water molecules would supply hydrogen bonds to stabilize the hydrolyzed metal cations in water,[38] the polarization of adjacent cluster water molecules would enhance the stability of metal cations in M⋯OH species through hydrogen bonding. A tantalizing catalysis of redox-inert hafnium(IV) was found for the oxy-functionalization of active methylene compounds in water (Table 4).[39] During the reaction, chlorine dioxide, a long-lived para-magnetic gaseous free radical, was generated, and it is considered to be a *bona fide* oxidant of this reaction. The reaction using TfOH instead of Hf(OTf)$_4$ suffered from low levels of conversion (<2%), suggesting a distinction between the role of hafnium(IV) and that of a Brønsted acid. The significant retardation of the reaction in both ethanol and aqueous acetonitrile, which can both solubilize sodium chlorite (entries 2 and 3), indicates the importance of water. Given that the structure of anhydrous Hf(OTf)$_4$ was reported to be built up of tetrameric $[Hf_4(OH)_8(OTf)_8]$,[40] it may adopt an exceptionally kinetically stable octahydroxohexadecaaquatetra-

Table 4. Water-Promoted Hafnium(IV)-Catalyzed Oxyfunctionalization of Active Methylene Compounds in Water
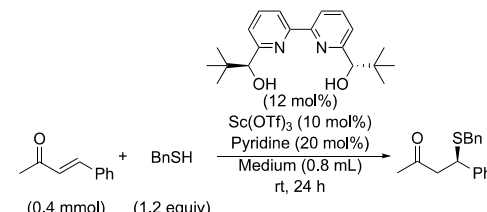

(0.9 mmol)

entry	medium	yield (%)[a]
1	H_2O	89
2	EtOH	49 (48 h)
3	CH$_3$CN/H$_2$O = 2/1	52

[a]Calculated based on crude ^{1}H NMR analysis.

hafnium (hafnyl) ion $[Hf_4(OH)_8(OH_2)_{16}]^{8+}$ in aqueous media. The presumable involvement of tetrameric hafnyl implies the pivotal role of hydroxo bridges or metal-bound water molecules in the activation of chlorine dioxide.

These examples indicate that although water is involved in the mechanism, it is not involved in the selectivity determination. The hydroxo scandium complex can be considered as an active species in thia-Michael addition in the presence of pyridine (Table 5).[41] Notably, the reaction run

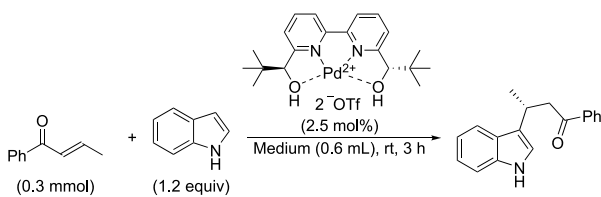## Table 5. Influence of Water in Enantioselective Thia-Michael Addition

(0.4 mmol)   (1.2 equiv)

entry	medium	yield (%)	ee (%)[a]
1	H_2O	84 (91)[b]	91 (91)[b]
2	CH$_2$Cl$_2$	93	28
3	THF	91	31
4	EtOH	88	63
5	PhMe	82	75
6	THF/H$_2$O = 9/1	54	64
7	EtOH/H$_2$O = 9/1	90	59

[a]Determined using HPLC analysis. [b]At 1 mol % catalyst loading.

in organic solvents or aqueous cosolvents suffered from decreased enantioselectivity. Considering the hydrolysis constant of Sc^{3+} (pK_h = 4.3), 4-fold amounts of pyridine were sufficient to form Sc(OH)$^{2+}$ along with polymeric hydroxy-bridged Sc$_2$(OH)$_2$$^{4+}$. The observation of a positive nonlinear effect also supports the formation of a hetero-oligomeric complex. The catalyst loading can be reduced to 1 mol % without loss of enantioselectivity.

The immense role played by water in determining enantiocontrol was also revealed for palladium-catalyzed indole C−H functionalization via the putative σ-indolylpalladium intermediate (Table 6).[42] Notably, substrates reacted in a highly enantioselective manner in water despite being immiscible (Type IIIa reaction). The reaction suffered from a significant reduction of enantioselectivity when run either in organic solvents or under solvent-free conditions. The incubation of the catalyst with indole in water plays a prominent role in achieving a high level of stereocontrol. Incubation under anhydrous conditions led to a significant

Table 6. Water-Controlled Enantioselectivity Switch in Type IIIa Indole C−H Functionalization[a]
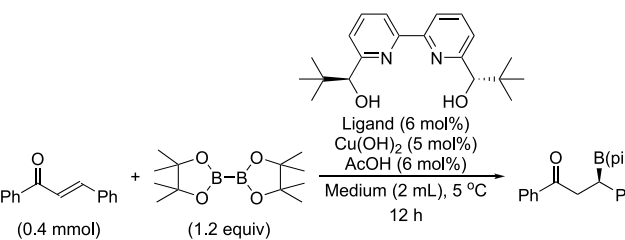

entry	medium	yield (%)	ee (%)[b]
1	H$_2$O	97	90
2	^{n}hexane	95	31
3	CH$_2$Cl$_2$	80	34
4	toluene	94	16
5	THF	92	1
6	Et$_2$O	72	0
7	EtOAc	77	1
8	DMSO	NR	
9	acetone	44	1
10	MeCN	90	1
11	MeOH	91	2
12	−(neat)	95	12

[a]NR = no reaction. [b]Determined using HPLC analysis.

decrease in enantioselectivity (61% ee) even though the reaction was performed in water. The rapid, quantitative, and exclusive deuterium exchange at the C3 position of indole in D$_2$O and contrasting lack of a corresponding D incorporation in organic solvents denote the efficient electrophilic palladation that is triggered by the aqua complex. The feasible electrophilic activation of a carbonyl or soft π-bond would provoke the C3-alkylation of indole in aprotic solvents without forming the σ-indolylpalladium intermediate. It is noted that the addition of even small amounts of organic solvents disabled stereoselective catalysis because the aqua complex preferentially undergoes water exchange reaction with these organic solvents with consequent loss of performance.

◼ TYPE IIIc REACTIONS

Although counterintuitive and difficult to predict, water upregulates catalytic activity in some Type IIIc reactions in which the substrates, catalyst, and water are immiscible with one another. The pivotal role of water is clear for the enantioselective β-borylation of chalcone (Table 7).[43] Notably, in this case, all the components involved are solid, and all are practically insoluble in water. The reaction, therefore, proceeds heterogeneously on the surface of chirally modified Cu(OH)$_2$ (entry 1), whereas the reaction did not proceed at all in typical organic solvents in which both substrates are soluble (entries 2−8). The reaction proceeded sluggishly in alcohols with a quite low enantioselectivity (entries 9 and 10) and failed to give the desired adduct under neat (solvent-free) conditions (entry 11). In addition, the inclusion of aqueous cosolvents resulted in a significant decrease in enantioselectivity (entries 12 and 13). A simple filtration after the first run confirmed the heterogeneity of the active form of the catalyst; the Cu content in the filtrate was less than the detection limit of the ICP equipment (5 ppb), and the filtrate did not show any catalytic activity. Extensive investigations identified water-soluble Cu-(OAc)$_2$ as an alternative to water-insoluble Cu(OH)$_2$, affording the product with slightly higher enantioselectivity. Notable is the exceptionally high turnover with the Cu(OH)$_2$

**Table 7. Water-Enabled Type IIIc Asymmetric β-Borylation**[a]

entry	medium	yield (%)	ee (%)[b]
1	H$_2$O	83	81
2	toluene	NR	
3	CH$_2$Cl$_2$	NR	
4	DMF	NR	
5	DMSO	NR	
6	THF	NR	
7	Et$_2$O	NR	
8	MeCN	NR	
9	EtOH	1	
10	MeOH	17	29
11	−(neat)	NR	
12	H$_2$O/THF = 1/4	77	79
13	H$_2$O/MeOH = 1/1	82	49

[a]NR = no reaction. [b]Determined using HPLC analysis.

catalyst, which reaches up to 43 200 h^{-1} at 0.005 mol % catalyst loading in a gram-scale reaction, the highest value in β-borylation reported to date. In addition, the Type IIIc conditions were applicable to β-borylation of water-sensitive α,β-unsaturated imines with perfect enantioselectivity.[44] Unusual Type IIIc catalysis using Cu(0) powder for enantioselective β-borylation is also noteworthy.[45]

Because Cu(OH)$_2$ possesses a layered structure where the hydroxide ligands in the plane are either doubly or triply bridging, a hydroxide-bridged multicopper complex is presumed as an active species. The mode of Type IIIc reactions based upon this architecture allowed unprecedented 1,6-borylation in a highly enantioselective manner (Scheme 2).[46] Considering that the copper is expected to activate the

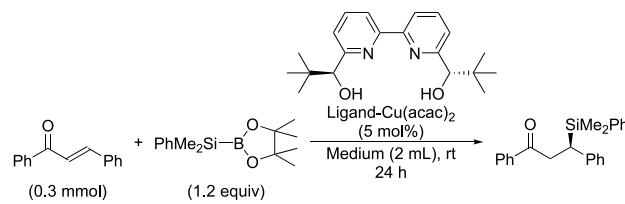**Scheme 2. Uncommon Asymmetric 1,6-Borylation under Type IIIc Conditions**
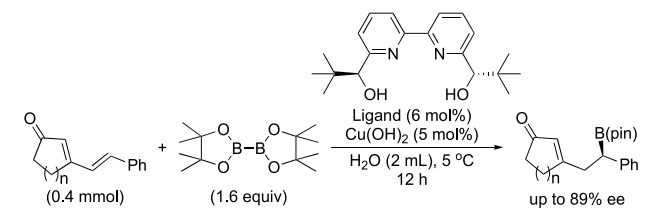
carbonyl group of cyclic dienones and to mount boron on their γ-position with high enantioselectivity, a monomeric copper complex is sterically not feasible. Indeed, cyclic dienones underwent a remarkable switch of regioselectivity from 1,6- to common 1,4-borylation in the presence of water-soluble monomeric Cu(OAc)$_2$.

Enantioselective β-silylation was enabled by acicular purplish crystals comprising Cu(acac)$_2$ and a chiral 2,2′-bipyridine ligand under Type IIIc conditions (Table 8).[47] In striking contrast to the Type IIIc reaction, the use of organic solvents,

> Although counterintuitive and difficult to predict, water upregulates catalytic activity in some Type IIIc reactions in which the substrates, catalyst, and water are immiscible with one another.

Table 8. Water-Enabled Type IIIc Asymmetric β-Silylation[a]

entry	medium	yield (%)	ee (%)[b]
1	H_2O	92	93
2	toluene	NR	
3	CH_2Cl_2	NR	
4	DMSO	NR	
5	THF	NR	
6	Et_2O	NR	
7	EtOH	4	0
8	MeOH	22	31
9	−(neat)	NR	
10	H_2O/THF = 1:4	73	6
11	H_2O/THF = 1:1	75	6
12	H_2O/THF = 4:1	88	72
13	H_2O/MeOH = 1:4	76	37

[a]NR = no reaction. [b]Determined using HPLC analysis.

alcohols, and even aqueous organic cosolvents gave inferior results in both yield and enantioselectivity. Notably, the reaction did not proceed at all in most cases including solvent-free conditions. The centrifugation of the reaction tube after the first run allowed separation of the reaction mixture into aqueous, organic, and solid phases, which delineates the technical advantage of Type IIIc reactions over conventional chemistry. A sharp increase in enantioselectivity correlated with a decrease in solubility of the catalyst is insightful (entries 10−12). The success of this chemistry may be built upon higher aggregation states associated with the insoluble catalyst. The advantage of the reactions lies in the application to enantioselective β-silylation of β-nitrostyrenes that remains still unrivaled (Scheme 3).

**Scheme 3. Type IIIc Asymmetric β-Silylation of β-Nitrostyrene**
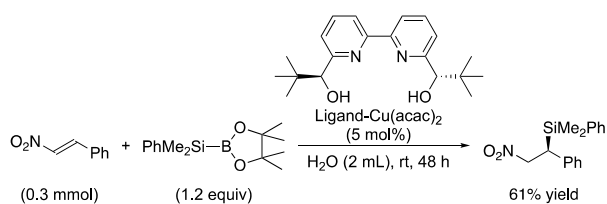
■ NEW FRONTIERS AND CHALLENGES IN SYNTHETIC ORGANIC "AQUACHEMISTRY"

Since the 18th century, the position of water in organic chemistry has changed too vertiginously. Marginalized once with organometallic chemistry flourishing, water has recently been spotlighted as a green reaction medium to realize clean chemical processes with an aid of surfactants or cosolvents. The early observation of "on-water" acceleration united synthetic chemists with aqueous media, and surfactant-based approaches are prospering to fulfill our synthetic needs. Aside from this, catalytic reactions in water that rely on neither cosolvents nor surfactants have been sporadically reported especially in the past decade. As amazing as it is, the "aquachemistry"[49] enables us to do more with less. As evidenced by chirality amplification in confined water cages,[48] water-induced hydrophobic amplification may result in enhanced enantioselectivity. Assembled with hydrogen-bonding catalysis, the hydrophobic hydration effect may provide new strategies to find out new catalytic reactions. Metal-bound water molecules form much stronger hydrogen bonds than bulk water molecules and may confer a pronounced Brønsted acidity. Corresponding hydroxo metal complexes formed after deprotonation may serve as Lewis acid/Brønsted base hybrids. They prove their superior worth in reactions involving CMD, radical activation, and σ-metathesis. Although the role of water remains elusive in many aspects, the examples outlined herein represent a broad perspective of synthetic organic "aquachemistry" that may ameliorate some problems that have plagued researchers so far or allow the invention of new reactions.

The pluripotent power of synthetic organic "aquachemistry" can be further elaborated. For instance, in organic electro-chemistry, aqueous electrolytes have the advantages of high ionic conductivity and noncorrosiveness compared with organic electrolytes, in addition to the clear general benefits of using water. Representative electrochemical Type III reactions include Kolbe electrolysis[6] and Zn-mediated Barbier-type electrochemical allylation.[50] Ackermann and co-workers reported an illuminating Type IIIa reaction under electrochemical conditions in a simple undivided cell with a platinum cathode and a reticulated vitreous carbon (RVC) anode.[51] Although the oxidation potential of $Co(OAc)_2$ is lower than that of the starting benzamide, in methanol competitive C−H oxygenation takes place. Unlike catalyst-free Type III reactions, the combination between synthetic organic electro- and aquachemistry is still in its infancy. Despite its narrow potential window, electrochemical Type III reactions using catalysts have the potential to enable transformations that exhibit the unique characteristics of both electrochemistry and "aquachemistry."

By and large, the further development of synthetic organic "aquachemistry" requires that entire data sets need to be examined. In-depth mechanistic and kinetic studies are imperative to elucidate the role of interfacial water molecules in catalytically accelerated Type III reactions and to theorize synthetic organic "aquachemistry", a field that still has a long way to go. The main reason for the lack of kinetic data in these reactions stems from the technical difficulties involved in establishing reproducible control of overall interfacial areas, surface to volume ratios, and droplet sizes in the reaction mixtures. Given that the physicochemical properties of droplets are highly dependent upon the nature of the

Table 9. Water-Promoted Type IIIa Electrochemical Alkyne Annulation
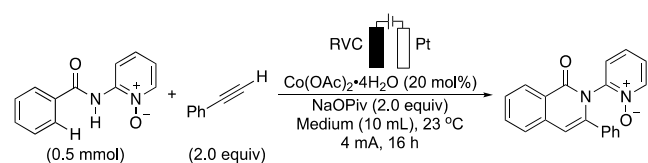
entry	medium	yield (%)
1	H$_2$O	64
2	HFIP	19
3	TFE	50
4	DMSO	31
5	MeOH	64 (17)[a]

[a]The yield of the C—H oxygenated product.

components, including viscosity and melting point, they need to be determined as a time-dependent dynamic parameter. On a laboratory scale, these parameters are also governed by both the stirring method and the size of the reaction flask. Recent progress has leveraged the development of interface-sensitive spectroscopic techniques. Adoption of the microfluidic technique enabled the influence of the water surface on catalyst-free Type III reactions to be quantified[52] and was even used to analyze the effect of droplet size on the enantioselectivity in a cinchonine-catalyzed Type IIIb reaction.[48] Nevertheless, a biphasic system is required to generate a precisely defined monodisperse water phase. Although electrospray ionization techniques have also been used in kinetic studies of catalyst-free Type III reactions,[53] microdroplet chemistry is distinct from Type III reactions.

Direct analysis in real time mass spectrometry (DART-MS) methods with isotopically labeled indicators has emerged recently as a complementary way to analyze catalytically accelerated Type III reactions directly and semiquantitatively.[54] DART-MS is based on atmospheric-pressure, soft, and robust ionization pathways, thereby allowing versatile applications that are not possible with electrospray ionization. The use of isotopically labeled indicator can significantly improve the reproducibility of the measurements by compensating for signal fluctuation and matrix effect that is usually ineluctable for ambient ionization techniques.[55] Nevertheless, this analytical method presupposes an even distribution of the components in the reaction mixture, including isotope effects on the diffusion process, thereby suffering from poor reproducibility for catalytically accelerated Type III reactions, especially when the starting material or product is solid. Hence, the development of a quantitative analysis technique that does not need an aliquot of the sample is coveted to deepen understanding of "aquachemistry."

Quantum mechanics/molecular mechanics (QM/MM) approaches are often used to understand catalyst-free Type III reactions, and a few examples of organocatalytic reactions have been reported.[56] The difficulty of calculating catalytic reactions lies in the fact that the structural fluctuation of a catalyst and its surroundings in aqueous environments, because of hydration, significantly multiplies the number of transition states en route to the desired product. Although the artificial force-induced reaction (AFIR) method enabled the challenging systematic sampling of transition states to determine the stereochemical information on the reactions performed in aqueous media,[57] there has been no QM study on catalytically

accelerated Type III reactions at the interface. This is because it is too computationally expensive to calculate reaction pathways involving interfacial water molecules. Thus, theoretical advances that significantly reduce the calculation costs are required.

In sharp contrast to conventional organic reactions in which the reactants are in solution, the bizarre nature of catalytically accelerated Type III reactions has so far thwarted attempts to completely elucidate their details using existing theory and techniques. Nevertheless, we believe that the very elusive nature of the underlying processes that are inherent to this chemistry belies the great potential for reaction invention and the expansion of organic synthesis in new, vibrant, and creative directions.

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Notes

The authors declare no competing financial interest.

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