HPMC: A Biomass-Based Semisynthetic Sustainable Additive Enabling Clean and Fast Chemistry in Water

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Abstract: The two types of water chemistries are (i) *on water* and (ii) *in water*. The fundamental understanding of "on water" chemistry is very well known. In contrast, "in water" chemistry is yet not well understood. Micellar catalysis is a major enabler of "in water" chemistry, while HPMC (hydroxypropyl methylcellulose)-based chemistry is new, and therefore, underdeveloped. This perspective is dedicated to "*in water*" chemistry of HPMC. Chemistry/catalysis in aqueous HPMC has recently been reported by AbbVie and our group. Using HPMC for "*in water"* chemistry requires basic knowledge of necessary procedures and limitations of this technology. Therefore, this perspective focuses on educating the audience about how HPMC can be effectively used in chemo-catalysis. Besides, it includes how and why the viscosity of HPMC is a critical factor for reaction's success. We also list the viscosity of various grades of commercially available HPMC, so readers could easily pick the supplier that provides the material of interest.

KEYWORDS: Sustainable Solvent, Biomass, Green Chemistry, Fast Reactions, HPMC

INTRODUCTION. Synthetic chemistry has grown to the levels for which its progenitors would have never imagined. Many new catalysts, transformations, and technologies have opened new doorways for rapid access to molecules of interest in the last two decades. In addition, novel technologies related to synthetic chemistry, polymer science, drug discovery, drug delivery, and nanoscience have led to new interdisciplinary fields. These advances in synthetic organic chemistry have also raised awareness of the environmental footprints of chemical processes.[1-5]

The released chemical waste to the air, land, and water has decreased between 2004 and 2013, which doesn't include the undocumented waste or volatiles from academic laboratories.[6] As per US EPA (Environment Protection Agency), the reduction in the release of chemical waste is mainly because of green chemistry and engineering practices.[7,8] While shedding light on this data, Constable critically stated that "the reductions highlighted by EPA are still largely related to process changes, and don't necessarily indicate that the underlying synthetic chemistry has changed significantly."[6] Changes in third-generation commercial processes could even result in more significant decreases in chemical waste. Therefore, a higher reduction in chemical waste is anticipated in the coming years. ACS Green Chemistry Institute,[9] REACH (Registration, Evaluation, Authorization and Restriction of Chemicals),[10] CHEM21 (Chemical Manufacturing Methods for 21st Century),[11,12] and EPAs[13] are pivotal in educating the chemistry community by promoting the 12 principles of green chemistry.[14,15]

Frequently, researchers misleadingly perceive green chemistry as just a modification of existing chemical processes. However, green chemistry's goal is to decrease chemical waste through innovation, not modification.[15] The innovation includes the discovery of non-conventional but greener transformations via mimicking Nature, removing toxic solvents from at least newer valuable transformations, focusing on target-based research instead of waiting for serendipity, implementing evolutionary processes in existing syntheses, and designing chemical reactions while considering long-term sustainability.

According to the ACS Green Chemistry Institute, solvents used in reactions and processes generate enormous waste.[9] Besides the negative impact on the environment, petroleum-based organic solvents are non-renewable. Nature is the best guide, utilizing water exclusively as the reaction medium in a renewable fashion.[16] As per Pfizer's solvent selection guide, water is the most preferred and greenest reaction "solvent."[17,18] Although it has many exciting features to offer including better and cleaner chemistry, it is predominantly used for reaction workups in organic synthesis. Sheldon's statement *"the best solvent is no solvent, but if a solvent is needed, then water has a lot to recommend it"*[19] has experimentally been proven correct in micellar catalysis, a significant enabler of chemistry in water.[20-24] Many notes and reviews have recently appeared in the literature on micellar catalysis;[25-30] therefore, it is not a topic of discussion here. Recently, HPMC (hydroxypropyl methylcellulose),[31] a cellulose-based additive, has also emerged as a significant enabler of chemistry in water through hydrophobic effects (Figure 1). Although only a small number of reports on reactions in aqueous HPMC are available,[31-34] this technology has enormous potential, if further investigated and developed. Thus, this perspective focuses on aqueous HPMC as a sustainable reaction medium and reaction rate booster.

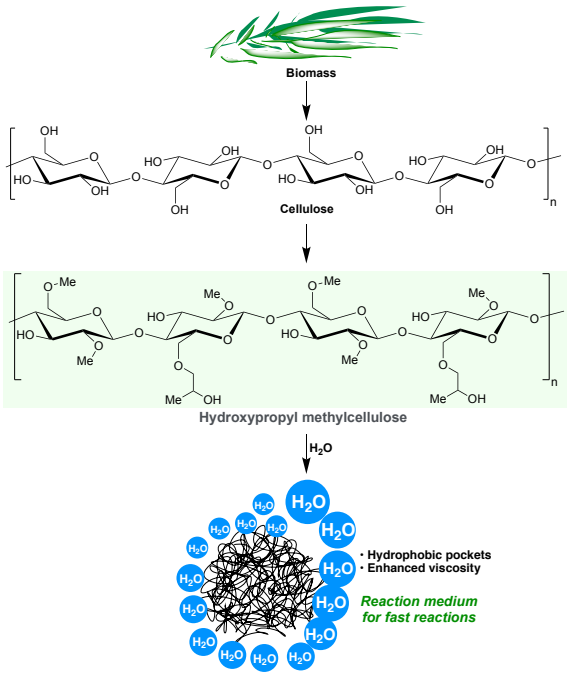
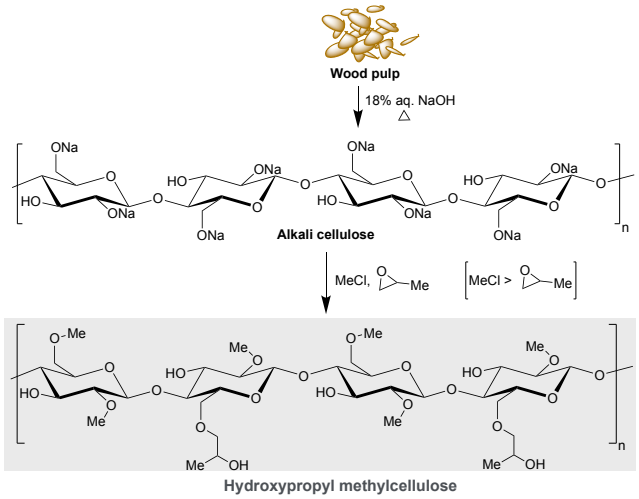


Figure 1. Hydroxypropyl methylcellulose in water as a sustainable reaction medium.

HYDROXYPROPYL METHYLCELLULOSE. HPMC, also called hypromellose, is a semi-synthetic polymeric organic compound derived from cellulose, a major component of biomass. Molecular weight of the polymer chain varies with the number of repeating units (n), ranging from 13,000 (n = 70) to 200,000 (n = 1000). It is an off-white powder soluble in cold water and forms a gel-like material when heated in water at 90 °C. It is broadly used as an emulsifier,[35] protective colloid,[36] and thickener in the food industry.[37] It is also a US FDA-approved inactive pharmaceutical ingredient for oral, nasal, ophthalmic, and topical drugs.[38] It is biodegradable, hydrophilic, and soluble in dipolar-aprotic solvents.[39,40]



Scheme 1. HPMC synthesis from wood pulp.

Although it is not clear when HPMC was first commercially introduced, its first synthetic method was reported in 1960.[37] Its synthesis includes treating purified wood pulp with 18% aqueous NaOH to obtain alkali cellulose, followed by reacting with methyl chloride and propylene oxide, respectively (Scheme 1).[37,41] The degree of substitution of HPMC with methoxy and hydroxypropoxy groups generally varies, which determines the physical properties of the resulting material. Its water solubility and swelling in water depend upon the methoxyl:hydroxypropyl ratio.

HPMC-WATER INTERACTION. The grade of HPMC is determined by the ratio of methoxyl and hydroxypropyl groups on the cellulose backbone. HPMC used in matrix tablets contains significantly more methoxyl substitution compared to hydroxypropyl.[42] Most commonly used HPMC types in pharmaceutics are HPMC 2208, HPMC 2906, and HPMC 2910.[43] In their numeric numbers, the first two denote the average of methoxyl groups. The last two numbers indicate average hydroxypropyl groups, *e.g.,* HPMC 2910 contains an average of 29 methoxyl and 10 hydroxypropyl groups.

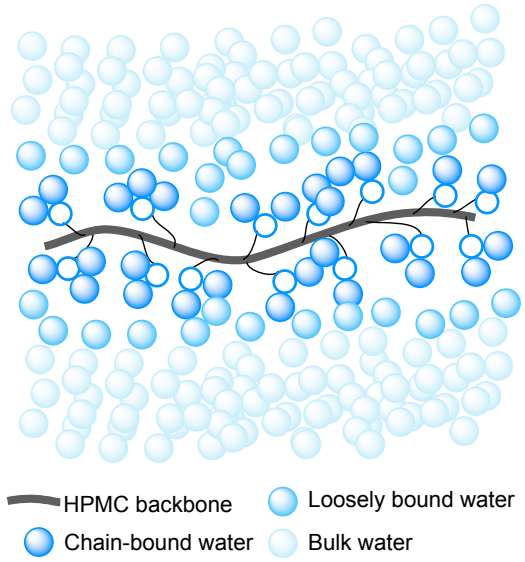


Figure 2. HPMC-water interaction: three types of water in aqueous HPMC solution.

HPMC 2906 and 2910 generally do not quickly hydrate,[44] and therefore, may not be good choices as reaction media. Small-sized particles of HPMC get swiftly hydrated. A commercially available HPMC generally contains an enormous amount of absorbed water in its amorphous state. Literature report state that upto 31% water (w/w) can be present in solid HPMC.[45] Likewise, depending upon the substitution pattern, the surface tension of 2% (w/w) aqueous solution of HPMC is 42-56 dyn/cm, and pH ranges from 5.5 to 8.0.

Water generally interacts with HPMC in two different ways in an aqueous phase: (i) HPMC chains-bound water, which cannot be frozen at 0 °C; (ii) loosely bound water that is present between bulk water and chain-bound water (Figure 2). The overall dissolution of HPMC in water is an exothermic process by *ca.* –33 cal/g.[46] The amount of water bound to the chains plays a critical role in using aqueous HPMC as a reaction medium. Therefore, the surface area of amorphous HPMC is a critical factor while selecting HPMC for chemistry in water. The higher the surface area is the better.

REACTIONS IN AQUEOUS HPMC MAY REQUIRE MILD HEATING. Although aqueous micellar catalysis

broadly works at room temperature, organic transformations in aqueous HPMC tend to work best under mild heating (Figure 3A).[31] The main reason for gentle heating is the formation of hydrophobic pockets in aqueous HPMC. In its aqueous solution, HPMC exhibits reversible gelation upon heating (Figure 3B). Upon heating, dehydration in the polymer interior occurs,[47] followed by hydrophobic interactions in the chain-substitution sites, leading to coiling and the formation of hydrophobic pockets to enable organic transformations. By contrast, polymer chains are fully hydrated at low temperatures, and interactions between polymer chains are limited. With the increase of temperature, initially, the viscosity of the aqueous solution decreases due to the dehydration process, followed by a sharp rise (at thermal gelation temperature) due to hydrophobic interactions.

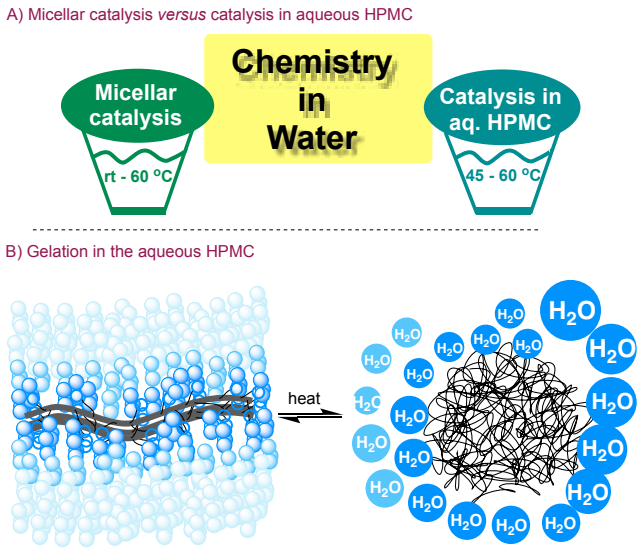


Figure 3. Mild heating triggers efficient catalysis in aqueous HPMC.

PRODUCT ISOLATION. If the concentration of HPMC in water is higher than 0.2% (w/w), product isolation can be difficult.[31] In such cases, extraction with methylene chloride (CH_2Cl_2) affords efficient product isolation, or otherwise, adding aqueous sodium sulfate facilitates extraction with ethyl acetate (EtOAc). With lower HPMC content, the strength of the gel layer is weak, and solvent diffusion is prominent to rupture the gel to release the product from the interior (Figure 4). Product precipitation has also been noted at lower concentrations (0.1 w/w) after reaction completion, avoiding organic solvents for extraction. When the product is either not solid or does not precipitate out after reaction completion, a gentle extraction with EtOAc enables product isolation if HPMC is used in low concentrations. HPMC stays in the aqueous phase after liquid-liquid extraction with EtOAc or MTBE. Likewise, metal catalysts or nanoparticles stay in the aqueous phase unless excess CH_2Cl_2 is used in liquid-liquid extraction. Notably, the type of HPMC used also determines the ease of product extraction. Based on research conducted in our labs, high viscosity grade HPMC causes trouble in product isolation, requiring excess CH_2Cl_2. Therefore, low viscosity HPMC in a concentration < 0.2% (w/w) is preferred.

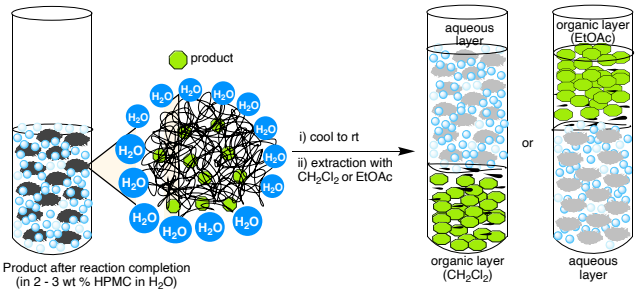


Figure 4. Product extraction from aqueous HPMC.

The chemistry in aqueous HPMC is thought to proceed in two ways: (i) at the interface of the water-polymer chain, (ii) in the hydrophobic pockets of HPMC. The first mechanism is more prominent when reactants are more crystalline and polar, while the second mechanism is favored at a high concentration of HPMC for less polar reactants.

AQUEOUS HPMC AS A REACTION MEDIUM. Unlike a micellar medium, an aqueous HPMC solution should not be aged for the reaction catalyzed by an organometallic catalyst. In aged solution, more swelling or gelation is observed, especially in 3 wt % solution, which partitions the catalyst and polar reactants. In an ideal case, a few hours total time is preferred. Slow addition of HPMC powder in deionized water at rt provides a clear solution for use. 0.1 – 0.2 wt % solution is preferred; otherwise, product extraction may require more organic solvent.

Table 1. Viscosity data of commercially available HPMC[a]

Commercial name	supplier	Viscosity (cps)
Mantrocel E5 2910	Parmentier	4-6
Hydroxypropyl methylcellulose 40-60	Sigma-Aldrich	40-60
Hydroxypropyl methylcellulose 40-60	Alfa Aesar	40-60
Hydroxypropyl methylcellulose 80-120	Sigma-Aldrich	80-120
Hydroxypropyl methylcellulose 2600-5600	Sigma-Aldrich	2,600-5,200
Methocel E4M Premium EP	Colorcon GmbH	3,000-5,600
Mantrocel K4M	Parmentier	4,100

[a]Viscosity values directly taken from supplier's website.

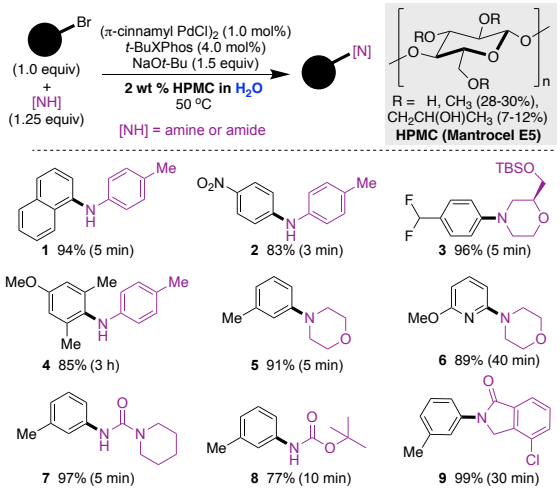
CAUTIONS IN USING HPMC AS A REACTION MEDIUM. For leveraging HPMC's effect as a reaction booster, do not heat a neat aqueous solution. Add all reaction components to the aqueous HPMC before heating. Avoid heating a reaction mixture above 65 °C, as it causes fast gelation and forms large particles,[48] which potentially trap the organometallic catalyst. Likewise, avoid annealing of the reaction mixture. For transformations containing lipophilic reactants, the higher the ratio of hydroxypropyl to methyl in the polymer enables faster reaction rates. The grade of HPMC is a critical factor for success of this aqueous technology. In terms of product extraction and better reaction kinetics, a low viscosity polymer was

found better than the high viscosity. The viscosity of commercially available HPMC is listed in Table 1.

TRANSFORMATIONS IN AQUEOUS HPMC. In a patent application from 2017 by AbbVie[34], Braje and co-workers demonstrated the use of aqueous HPMC for several reaction types on a limited number of substrates (2-3 for each reaction class), including Buchwald-Hartwig aminations, palladium-catalyzed amidation and carbamate-forming reactions of aryl bromides, and Suzuki-Miyaura, Sonogashira, Heck, and Stille couplings. In the same document, a few examples of ruthenium-catalyzed cross-metathesis, rhodium-catalyzed 1,4-addition of boronic acid to enoates, gold-catalyzed cyclization, palladium-catalyzed Miyaura borylation, Wittig reaction, Diels-Alder reaction, nucleophilic aromatic substitutions, amide bond formation, nitro reductions, and reductive aminations are also disclosed. The first detailed study on the functioning of HPMC was reported together in 2020 by our and Braje groups.[31]

HPMC IN WATER ENABLES EXTREMELY SHORT REACTION TIMES. To enable short reaction times, aqueous HPMC has shown promising activity. In collaborative work with AbbVie, we have demonstrated that the dissolution of organometallic palladium complexes in aqueous HPMC causes formation of small nanoparticles accommodated by hydrophobic pockets of HPMC.[31] These nanoparticles are ligated with a phosphine ligand and show better activity compared to their molecular counterparts. The enhanced solubility of nanoparticle catalysts and reactants in these hydrophobic pockets, controlled solution viscosity, and optimal Brownian movement significantly enhanced reaction rates for the amination and amidation reactions.

Table 2. Fast aminations and amidations in aqueous HPMC[a]



[a]Data taken from ref 31.

As the representative examples (9 out of 32) shown in Table 2 (**1**-**9**), reactions were extremely fast. Aromatic (**1**, **2**, **4**) and aliphatic (**3**, **5**, **6**) amines reacted in minutes. Likewise, amides (**7**-**9**) showed excellent reactivity. Notably, the reaction rate was comparatively slower with aryl bromides containing steric hindrance at the *ortho*- positions (**4**). However, this reaction time, *i.e.,* 3 h, is still relatively shorter than that in traditional organic solvents. At this stage of project development, we were unaware that a higher HPMC amount (2 wt %) causes difficulty in product extraction. Therefore, CH_2Cl_2 was used for product extraction from aqueous reaction mixtures. In this study, low viscosity (4-6 cps) HPMC was used.[31]

The rapid formation of ligated nanoparticles was noted when *t*-BuXPhos(π-cinnamyl)palladium chloride dissolved in aqueous HPMC. As observed in high-resolution transmission electron microscopic analysis, the nanoparticles' average size was *ca.* 1.5 nm (Figure 5A, B). The ligated nature of these nanoparticles was confirmed by a control ^{31}P NMR study (Figure 5C). The ^{31}P signal of the nanoparticle was observed at 26.45 ppm, which was different from the signals from unbound *t*-BuXPhos (22.01 ppm) and *t*-BuXPhos(π-cinnamyl)palladium chloride (53.82 ppm).

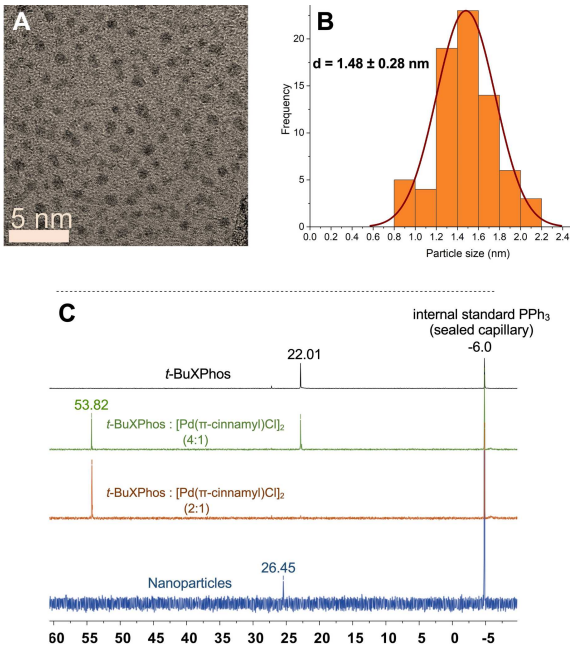
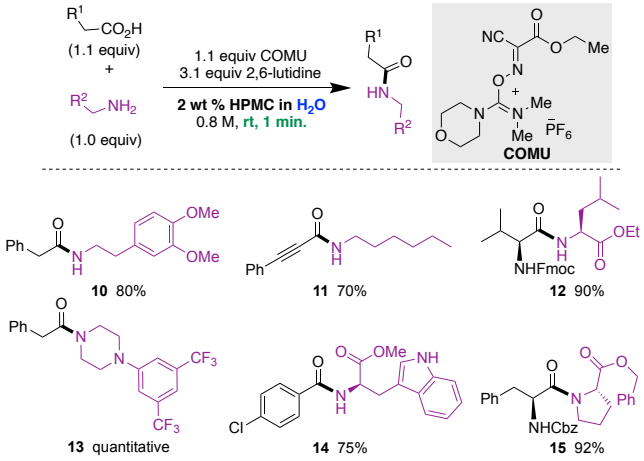


Figure 5. Nanoparticle catalyst characterization. (A) HRTEM (high-resolution transmission electron microscopy) image. (B) Particle size distribution. (C) Control NMR study evidencing nanoparticles ligated with *t*-BuXPhos. [Credit: *ACS Sustainable Chem. Eng.* **2020,** *8*, 12612−12617]

In the same report, we disclosed ultra-fast amide couplings. Reactions were completed within one minute for a broad range of substrates. Representative examples are highlighted in Table 3 (**10**-**15**). Couplings of alkylamines with non-aromatic (**10**-**13**, **15**) and aromatic (**14**) acids proceeded efficiently. Couplings were also demonstrated on 100-gram scale reactions, as well as a 4-step, 1-pot sequence (for details, see the original report).[31] Once again, due to the use of a higher weight percent of HPMC, the addition of a saturated solution of aqueous Na_2SO_4 was required, causing precipitation of HPMC and release of product into the EtOAc layer. This precipitation of HPMC circumvented extraction with harmful CH_2Cl_2.

Table 3. Ultrafast amide couplings in aqueous HPMC[a]

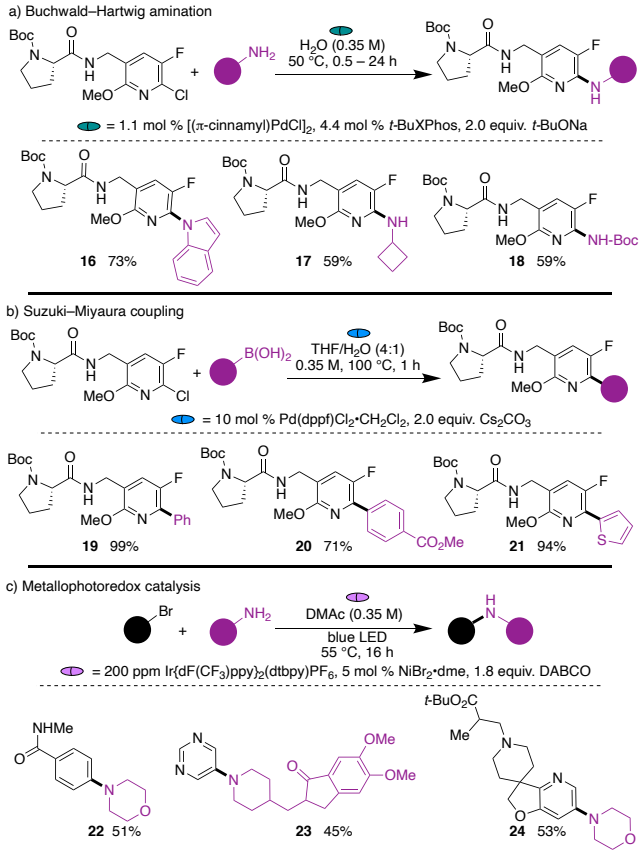


[a]Data taken from ref 31.

Other groups have demonstrated the applications of reagent-filled capsules to deliver sensitive reagents to chemical reactions.[49] These reagent capsules can be loaded with various air-sensitive catalysts, ligands, and bases, and can be used in reactions.[49-51] Along these lines, AbbVie has recently reported the use of inexpensive HPMC shells filled with catalyst and base, as reagent capsules for C–N and C–C cross-couplings.[32] HPMC capsules are cheap, readily available, compatible with hygroscopic reagents, and offer good protection to the catalyst and ligands from oxygen and water.[52] It has been reported elsewhere that HPMC capsules display protection against oxygen transmission (166 cc/m^2/day), their water vapor transmission rate is 263 g/m^2/day, and their shelf-life is 2 years at 25 °C and 65% humidity.[52] The catalyst, ligand, and base-filled HPMC capsules were explored on three transition-metal-catalyzed reactions, *i.e.,* Buchwald−Hartwig, Suzuki−Miyaura, and metallophotoredox C−N cross-couplings. The catalyst, ligand, and base were selected from already available literature reports for the respective transformations.[31,53]

The capsules for palladium-catalyzed C–N cross-couplings were prepared using [(π-cinnamyl)PdCl]$_2$ or [(allyl)PdCl]$_2$ as Pd source, *t*-BuXPhos or cBRIDP as ligand, and stoichiometric amounts of *t*-BuOK or *t*-BuONa as the base. Further, the activity of these capsules was explored for the amination of chloropyridine derivatives under mild aqueous conditions. These capsules successfully enabled the synthesis of *N*-arylated products with notable diversity in nitrogen nucleophiles, including alkylamines containing strained rings (**17**), heterocycles (**16**), and carbamate derivatives (**18**) (Table 4a). Moreover, the activity of these capsules was retained even after two months of benchtop storage. However, the shelf-life beyond a two-month period has not yet been studied.

Table 4. HPMC capsules for transition-metal catalysis[a]



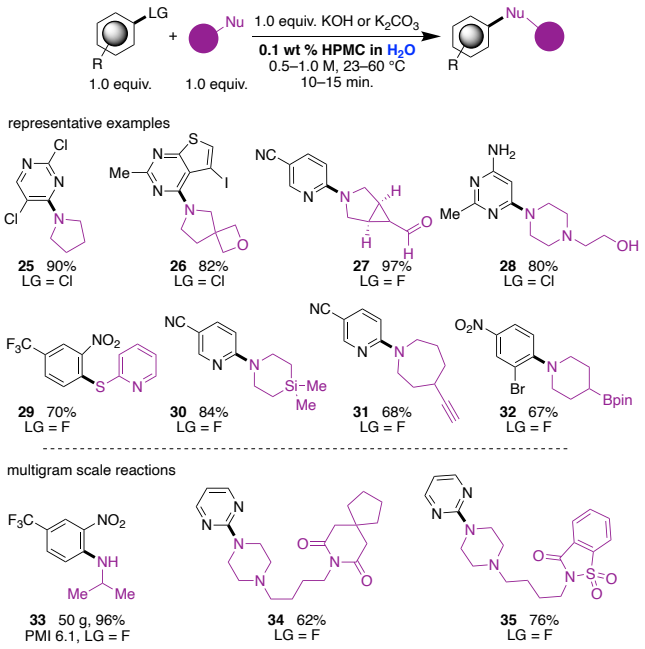
[a]Data taken from ref 32.

The technology was extended to Suzuki-Miyaura cross-couplings (**19**-**21**) using capsules filled with dppfPdCl$_2$•CH$_2$Cl$_2$ and Cs$_2$CO$_3$.

The HPMC capsule technology also enabled C–N bond formation via visible-light mediated photoredox catalysis.[32] The amine arylation via metallophotoredox catalysis originally developed by MacMillan and co-workers was selected as a benchmark transformation.[53] HPMC capsules filled with catalytic Ir{dF(CF$_3$)ppy}$_2$(dtbpy)PF$_6$, NiBr$_2$•dme, and stoichiometric amounts of DABCO were employed for the *N*-arylation of aryl bromides under blue LED irradiation (Table 4c, **22**–**24**). Primary and secondary alkyl amines reacted readily. The technology was also utilized to synthesize Donepezil analogs (**23**) and a drug-like molecule **24**. This capsule technology circumvents the operational complexity of catalyst weighing and provides an accessible alternative to stock solutions. Overall, this HPMC capsule technology is an effective chemical delivery system of air-sensitive ligands, catalysts, and reagents for various transition-metal catalyzed reactions.

Nucleophilic aromatic substitution reactions represent one of the most often used organic reactions in medicinal chemistry.[54-56] In collaboration with Abbvie, we recently explored the application of HPMC-derived hydrophobic pockets for S$_N$Ar reactions under mild aqueous conditions without using any additives or co-solvents,[33] The technology is compatible with various nucleophiles and has excellent functional group tolerance. The optimized conditions employ inexpensive KOH or K$_2$CO$_3$ as base with equimolar amounts of other reagents. The scope of this approach was tested in over 40 substrates, and representative examples are provided in Table 5.

Table 5. HPMC enabled S_NAr reactions in water



[% Yields data taken from Ref 33 with permission from the Royal Society of Chemistry].

This methodology has also shown unprecedented regio- and chemo-selectivities. In substrate **25**, the 2-position remained mostly intact (96:4) under aqueous HPMC conditions. By contrast, in DMF, the reaction yields a 65:29:6 mixture of 4-substituted, 2-substituted, and 2,4-disubstituted products, respectively.[33] Exceptional chemo-selectivity was observed in nucleophiles containing boron, oxygen, nitrogen, and silicon atoms. *N*-arylation was preferred over *O*-arylation, which was utilized in a synthesis of Dasatinib precursor **28**. Apart from nitrogen nucleophiles, a sulfur nucleophile was also found to be compatible (**29**). Nucleophiles containing spirocycles showed no side reactions (**26**, **27**). Substituted azasilanes (**30**) and a terminal alkyne bearing azapene (**31**) exhibited moderate-to-excellent reactivity. Notably, base-sensitive boronate esters (**32**) remained intact, as significant deborylation was not observed (<5%). On the other hand, in DMF, 25% deborylation was observed.[33]

The scalability was demonstrated on a 50 g scale reaction (**33**). The desired product was isolated in 96% yield without using organic solvent at any stage. The product was isolated by a simple filtration. The process mass intensity (PMI) was calculated to be 6.1, revealing the extent of greenness. This aqueous technology was further applied to synthesize anxiolytic psychotropic drugs such as Ipsapirone (**34**) and Buspirone (**35**). Most notably, a base-sensitive sulfonamide remained unaffected under these mild reaction conditions.

SUMMARY AND PROSPECTIVE. The HPMC-based aqueous technology has enormous potential, contributing to chemistry that lives up to and abides by the 12 Principles of Green Chemistry. Besides reaction rate acceleration, we have documented that the reactions of specific substrates, which do not proceed in organic solvents, work very well in aqueous HPMC (unpublished). This may be due to lowering the activation barrier through hydrophobic effects. HPMC-mediated reactions in water do not require any co-solvent that makes this "in water" technology especially attractive. Both micellar and HPMC technologies have the potential to provide new roadmaps for sustainable organic synthesis. Micellar technology has its own merits—it works in cases where HPMC technology fails and vice versa. Product isolation from micellar media never requires sodium sulfate or excess solvent. The product isolation in HPMC technology could be further eased by fine-tuning the ether linkages in the cellulose backbone, mainly by replacing the methyl groups with more lipophilic substituents. To address this issue, our group is working with AbbVie, results from which will be disclosed in due course.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Biographies

Sudripet Sharma is currently pursuing his Ph.D. degree under the supervision of Prof. Sachin Handa in the department of Chemistry, University of Louisville, KY, USA. He received his bachelor's degree in 2013 and master's degree in Organic Chemistry in 2015 from the Himachal Pradesh University Shimla, India. Sudripet then worked as a research associate in a drug discovery program in Chandigarh, India. In August 2018, he began his Ph.D. studies, and his research interests are sustainable photoredox catalysis, earth-abundant metals-based nanocatalysts, and chemistry in water.

Tharique N. Ansari received his integrated master's degree from Mahatma Gandhi University (India) in 2016. Subsequently, he joined the chemistry department at the University of Louisville to pursue doctoral studies under the guidance of Prof. Sachin Handa. His research focuses on developing a toolbox for the fundamental understanding of aqueous micellar

nanocatalysis, novel selective reaction pathways enabled by water-sensitive reaction intermediates in water, and sustainable catalyst development for cross-couplings.

Sachin Handa was raised in Patti, a small town of Punjab (India), where he completed his undergraduate studies. He received a Ph.D. degree under the guidance of Prof. LeGrande Slaughter in the USA, where his research focus was the development of nonracemic acyclicdiaminocarbenes. Subsequently upon completing postdoctoral training under Prof. Bruce H. Lipshutz at UC Santa Barbara, he started his independent career as an assistant professor at the University of Louisville in August 2016. In July 2021, he was promoted to associate professor with tenure. His research laboratory focuses on the development of sustainable catalysts and reaction pathways. He is a recipient of the 2018 Ralph E. Powe Junior Faculty Enhancement Award by ORAU, the 2018 Peter J. Dunn Award for Green Chemistry and Engineering Impact in Industry by the American Chemical Society, and the NSF CAREER Award.

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ABBREVIATIONS

HPMC, hydroxypropyl methylcellulose; US EPA, United States Environment Protection Agency; US FDA, United States Food and Drug Administration.

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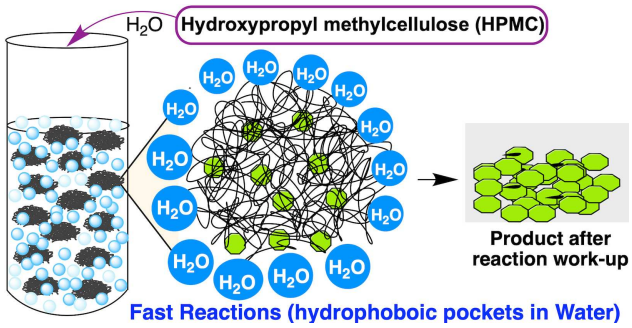

HPMC enables fast reactions in water as a sustainable and recyclable medium.