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Nucleophilic aromatic substitution reactions under aqueous, mild conditions using polymeric additive HPMC†

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The use of the inexpensive, benign, and sustainable polymer, hydroxypropyl methylcellulose (HPMC), in water enables nucleophilic aromatic subsitution (S_NAr) reactions between various nucleophiles and electrophiles. The mild reaction conditions facilitate a broad functional group tolerance that can be utilized for subsequent derivatization for the synthesis of pharmaceutically relevant building blocks. The use of only equimolar amounts of all reagents and water as reaction solvent reveals the greenness and sustainability of the methodology presented herein.

Introduction

The recent interest in using water as a reaction solvent for synthetic chemistry is built upon a desire for cheaper, less hazardous, and more sustainable production of chemicals. Besides, this increasing interest also reflects advantages that aqueous reaction conditions can offer in terms of selectivity, for example, due to the unique physical and chemical properties of water.[1] Pioneering work from Breslow and Grieco in the 1980s presented the starting point for an ever since broadening application of water as reaction medium for chemical reactions.[2,3] As solubility of organic compounds in this highly polar solvent remains the main obstacle, a variety of different methods to enhance aqueous solubility have been investigated.[4] The most promising approach so far relies on the use of non-ionic surfactants in water that form dynamic micelles of different sizes and shapes.[5–7] In these micelles, organic compounds can be solubilized, thereby allowing chemical reactions to proceed under mild reaction conditions.[8–10] The formation of these "nanoreactors"[11] copes not only with the low solubility of organic reactants in water, but also with the water sensitivity and associated decomposition of reactive intermediates, *i.e.* by hydrolysis. By employing micellar catalysis, chemical reactions have evolved from being conducted at the interface of insoluble organic reactants and water, termed "on water",[12,13] to taking place "in water".[14,15] Designer surfactants such as PS-750-M,[16–18] or TPGS-750-M[19,20] have shown to be broadly applicable to different types of reactions. Both surfactants are used for discovery research, *i.e.*, small-scale synthesis of drug candidates in the pharmaceutical industry.[21] Notably, TPGS-750-M has proven its generality by enabling syntheses of active pharmaceutical ingredients (APIs) also on industrial scale.[22,23] However, some of the designer surfactants are relatively expensive, and their synthesis requires several steps.[20] Besides, their shelf-life in aqueous solution can be diminished by the presence of labile ester groups, which are prone to hydrolysis.[24] Furthermore, co-solvents, such as THF, acetone, DMF, *etc.*,[25] are often required to achieve high reaction yields. The presence of these co-solvents generally ensures homogeneous reaction mixtures and uniform mixing, which is particularly necessary in scaled-up reactions.[26–28] The outcome of reactions depends on physical properties of the micelles, such as size, shape, critical micelle concentration (CMC), and their relative stability which can complicate the application of micellar catalysis.[11]

An alternative method for conducting chemical reactions in water using catalytic amounts of the inexpensive, benign, and sustainable polymer hydroxypropyl methylcellulose (HPMC, see Fig. 1), could be a solution to aforementioned issues. In contrast to micelle-forming non-ionic surfactants, the solubility enhancing properties of HPMC are hypothesized to originate from the formation of hydrophobic pockets.[29] This three-dimensional structure of HPMC enables amide couplings and Buchwald–Hartwig aminations without the need of organic co-solvents in unprecedented short reaction times.[29] However, the application of aqueous HPMC solution as solvent to other important reaction types remained unaddressed so far.

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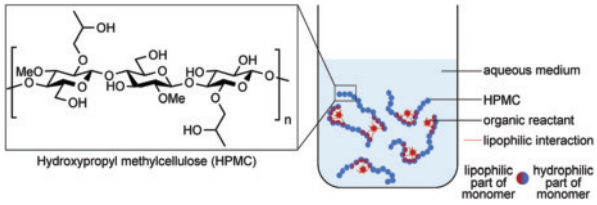


Fig. 1 Structure of hydroxypropyl methylcellulose (HPMC), originating from renewable cellulose, and its plausible mode of action (schematic).

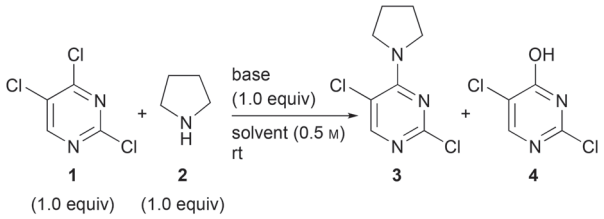
To further demonstrate the generality of this approach, nucleophilic aromatic substitution (S_NAr) reactions were investigated. S_NAr reactions are the second most frequently used reaction type in medicinal chemistry,[30] as evidenced by the high abundance of drugs that require at least one S_NAr reaction for their assembly.[31] Besides, S_NAr reactions possess a huge potential to be conducted under sustainable reaction conditions as they are not metal-catalyzed, and have an appealing atom-economy. Despite these advantages, they are commonly conducted in dipolar-aprotic solvents, such as, DMSO, DMF, DMAc, 1,4-dioxane, and NMP. These solvents account for a significant amount of waste produced by the pharmaceutical industry.[32] Likewise, some of these solvents, such as NMP, 1,4-dioxane, and DMF, present a significant health risk, and their increasing regulation and restriction of use point to the need for feasible alternatives.[33,34] From an energy and safety standpoint, the requirement of high temperatures (80–130 °C) at which S_NAr reactions are conducted is also a concern. Moreover, these harsh reaction conditions generally cause a reduced functional group tolerance due to unwanted side reactions. As a consequence, a protecting group strategy is often required, which can further complicate synthetic routes and is not desirable from an economic point of view due to an increased use of organic solvents and potentially toxic chemicals. Herein, we disclose a general, efficient, and sustainable methodology that addresses aforementioned challenges and meets the standards set by ACS Pharmaceutical Green Chemistry Institute for S_NAr reactions.[35] Our technology involves safe, mild, and environmentally benign reaction conditions leading to a striking functional group tolerance.

Results and discussion

Reaction optimization

Our investigation of the S_NAr reaction in aqueous medium using the polymer HPMC as an additive started by optimizing the reaction of 2,4,5-trichloropyrimidine (**1**) with pyrrolidine (**2**). As shown in Table 1, all reagents can be used in equimolar amounts (1 : 1), which significantly eases the purification of the resulting products, avoids using any excess of expensive or toxic chemicals, and thereby minimizes waste production. Several bases with different pK_a values were screened (see Table 1, entries 1–7). The formation of **3** increased when bases with higher pK_a values were used. Accordingly, reaction times decreased significantly from 30 minutes to 10 seconds, which

Table 1 Optimization of the S_NAr reaction in HPMC/H_2O



Entry	HPMC [wt%]	Base (pK_a)	Time [min]	Conv. [%]	Ratio 3 : 4
1	2	$NaHCO_3$ (6.0)[36]	30	70	n.d.
2	2	2,6-Lutidine (6.8)[37]	30	80	n.d.
3	2	K_2CO_3 (9.1)[36]	30	99	>99 : 1
4	2	DIPEA (10.8)[38]	30	99	n.d.
5	2	DBU (11.9)[39]	10 s	99	n.d.
6	2	KOH (15.7)[40]	10 s	99	>99 : 1
7	2	NaO*t*Bu (17.0)[40]	10 s	99	>99 : 1
8	1	NaO*t*Bu (17.0)	10 s	99	>99 : 1
9	0.1	NaO*t*Bu (17.0)	10 s	99	>99 : 1
10	0	NaO*t*Bu (17.0)	30	53	1 : 1
11	0.1	NaO*t*Bu (17.0)	10 s	99	4 : 1[a]
12	0.1	KOH (15.7)	10 s	90[b]	>99 : 1

Order of addition: 1. electrophile (**1**), 2. nucleophile (**2**), 3. base. Conversion of electrophile **1** and ratio of **3** : **4** determined by LC/MS. n.d.: not determined, s: seconds. [a] Changed order of addition: 1. electrophile (**1**), 2. base, 3. nucleophile (**2**). [b] Isolated yield.

was the minimal time detectable using LC/MS. From several organic and inorganic bases, DBU, KOH, and NaO*t*Bu were found to be equally effective in terms of yield and reaction time. However, due to cost, atom-economy, and superior safety profile, KOH was selected as the base of choice for further investigation of the substrate scope. Besides, we were also interested to explore whether different counterions of the hydroxide ion would be influenced differently by the surrounding free hydroxy groups of HPMC, *e.g.* by complexation. We hypothesized that this could result in altered distances between the ion pairs, and therefore, lead to modified base strengths of the corresponding hydroxide ion, affecting conversions as well as reaction kinetics. Moreover, the solubility of the inorganic salt, *e.g.* CaF_2, which is formed during the course of the reaction could have an impact on the reaction kinetics. To investigate these hypotheses, seven different hydroxides were examined (see ESI, Fig. S1†). This study revealed only minor effects on the reaction kinetics which could not be correlated to the ion association of the different ion pairs. A variety of lipophilic auxiliary bases were explored to examine if a beneficial impact on the reaction could be observed due to their ability to enter hydrophobic pockets formed by HPMC. For this purpose, different lipophilic silanols and phenols were screened, but no positive impact on the product formation or the reaction kinetics was observed (see ESI, Table S1†).

Next, we evaluated the minimally required amount of the solubilizing additive HPMC, and found that it is possible to reduce it from commonly employed 2 wt% surfactant for micellar catalysis[41] to 0.1 wt% (see Table 1, entries 7–9). A control reaction in pure water was conducted (see Table 1,

entry 10) and the conversion dropped to 53%. Additionally, side-product **4** resulting from the hydrolysis of 2,4,5-trichloropyrimidine (**1**) was formed in equal amounts as the desired product **3** when using sole water as reaction solvent. Interestingly, the remarkable regioselectivity for the 4-position was not affected (for further discussion see section Scope and limitations). Moreover, the order of addition of the reactants plays an important role in the side product formation. Altering the order of addition of reactants from 1. electrophile, 2. nucleophile, 3. base to 1. electrophile, 2. base, 3. nucleophile also led to an increased formation of the side-product **4** (see Table 1, entry 11).

Under the optimized reaction conditions, we finally obtained product **3** in 90% isolated yield (see Table 1, entry 12).

Subsequently, we compared our approach with different known methodologies for the S_NAr reaction of 2-fluoronitrobenzene (**5**) with benzylamine (**6**). We found that our methodology was as equally effective as the reaction in organic media (92%), and better than micellar technology (74%),[41] or "on water" (64%) (see Fig. 2). As DCM is not an environmentally friendly solvent,[42,43] its replacement for extraction of the S_NAr products was investigated. Notably, product extraction with minimal amounts of EtOAc results in comparable isolated yields (see ESI, Table S3†). Additionally, HPMC is not soluble in EtOAc leading to high purity of final products (see ESI, Table S4 and Fig. S3, S4†). On a small scale (0.5 mmol), products were mainly purified by column chromatography. However, on a large scale (20–50 g) compounds **8** and **9** were isolated by simple filtration, which completely circumvented the use of organic solvents (see Fig. 3). Besides, neither a reduction in isolated yield upon scaling the reaction up by a factor of 200–500 nor a possible side-reaction of the hydroxy group of **8** were observed. These remarkable aspects of the scale-up reactions are indicating an unproblematic transfer of our HPMC technology to process chemistry. To enable direct comparison of the methodology presented herein with other approaches, the process mass intensity (PMI), a metric to evaluate the sustainability of a process,[44] was calculated for both reactions on-scale and was found to be remarkably low (see ESI, Table S5†). Next, recycling of the aqueous reaction solvent containing HPMC was evaluated. In a recycle study, we performed three consecutive S_NAr reactions in the same reaction medium. Desired products **3** and **10** were obtained in good yields regardless of the reaction cycle (see Scheme 1).

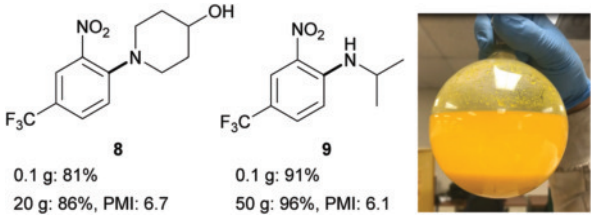


Fig. 3 Comparison of isolated yields on small scale (0.1 g) and large scale (20–50 g) for compounds **8** and **9**. PMI: process mass intensity. Picture: reaction mixture of compound **9** on 50 g scale.

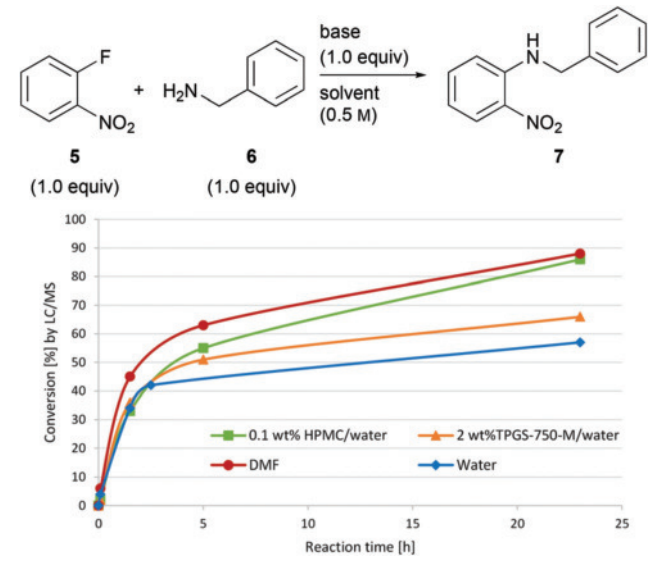
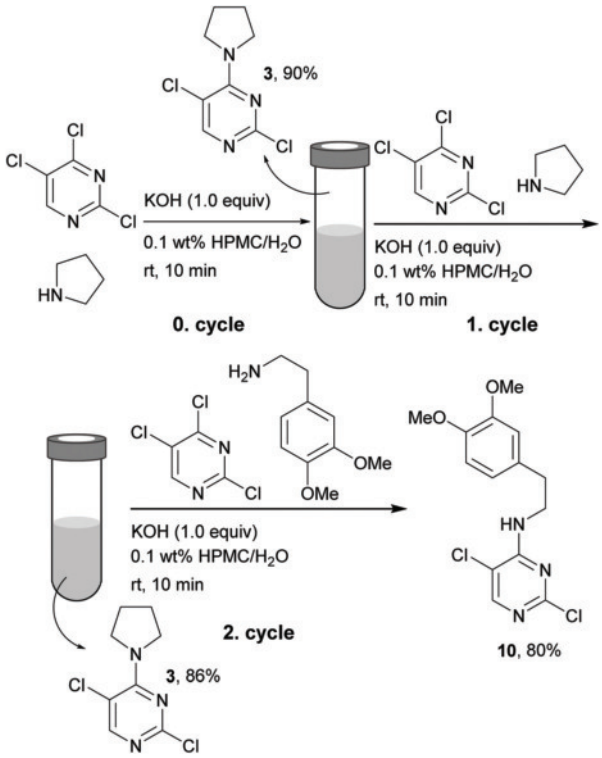


Fig. 2 Comparison of different methodologies for the S_NAr reaction of 2-fluoronitrobenzene (**5**) with benzylamine (**6**). The following bases were used for the reactions: 0.1 wt% HPMC/water: KOH (90%); 2 wt% TPGS-750-M/water: K_3PO_4 (74%); DMF: K_2CO_3 (92%); water: KOH (64%). Isolated yields are reported in brackets.



Scheme 1 Recycle study of the aqueous reaction solvent. Products were extracted from the reaction mixture using EtOAc and the aqueous layer was reused for the next reaction cycle (see ESI, page S9† for details). Reactions were performed on 1.0 mmol scale.

Scope and limitations

We applied the optimized reaction conditions to a large library of diverse substrates and reacted multiple electrophiles with a variety of different nitrogen-based nucleophiles at mild temperatures using a 1 : 1 ratio of the reactants along with the cheap, benign, inorganic base KOH (see Scheme 2). Within this substrate scope, we noted that several products were formed after unprecedented short reaction times (*e.g.* **14**, **40–46**, 10–25 min). We found that it is not only possible to react free amine moieties but also the corresponding HCl- or HBr-salts of the amines (**11**, **17**, **18**, **22**, **25–34**) by employing an additional equivalent of base. Benzylic (**7**, **35**, **40**), primary (**9**, **24**, **44**), and secondary amines (*e.g.* **14–23**) were reacted successfully including highly sterically hindered amines (**44**). Different cyclic secondary amines were reacted spanning ring sizes from four- to seven-membered rings. Remarkably, aniline derivative **13** which is significantly less nucleophilic than aliphatic amines was also reactive using our reaction conditions.

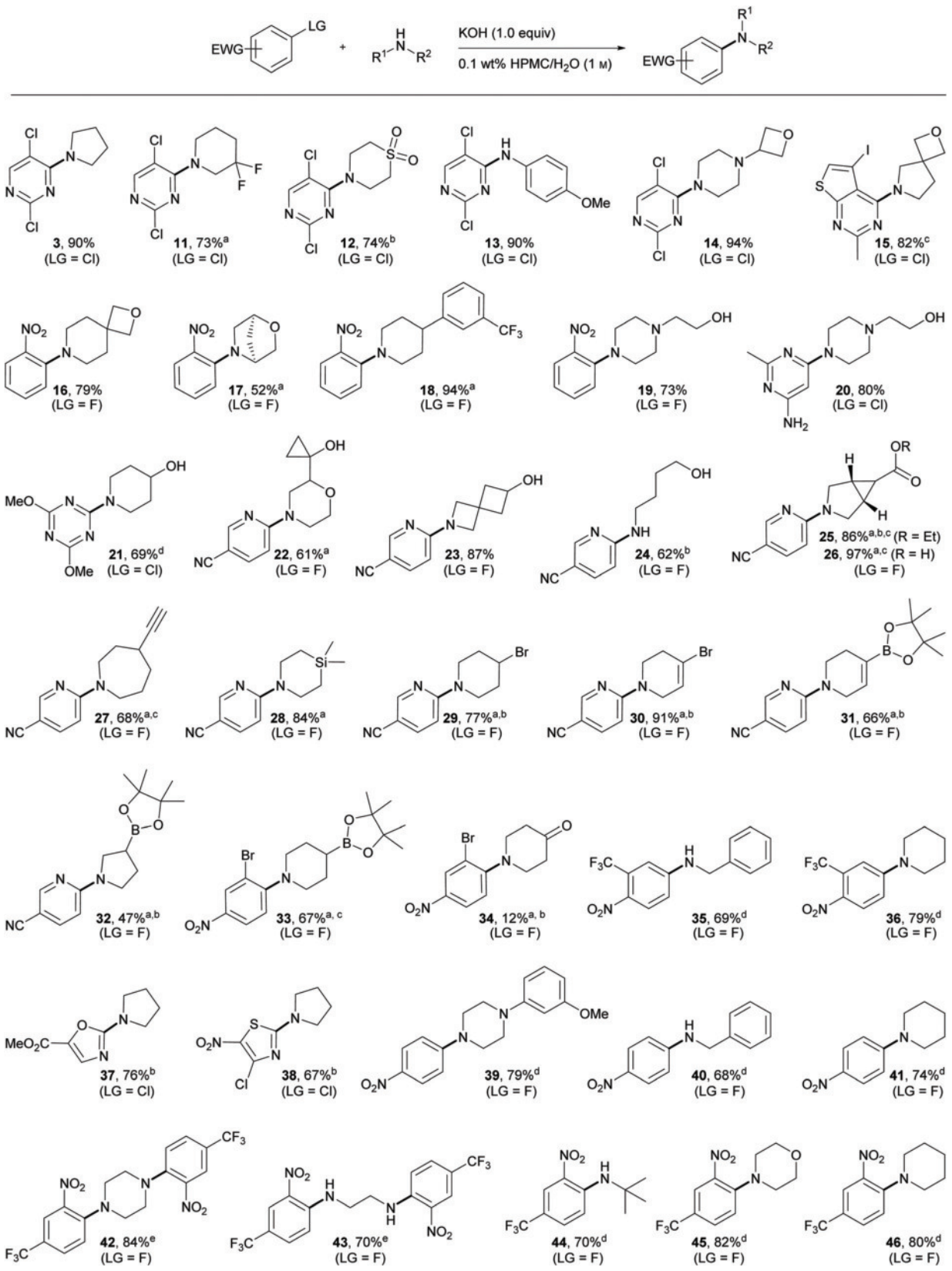
Several functional groups showed surprisingly good stabilities under aqueous basic reaction conditions including strained systems like oxetanes (**14–16**), which are prone to ring opening,[45] and different types of esters. Carboxylic esters (**25**, **37**) showed only a minimal amount of hydrolysis and were isolated in excellent yields if a weaker base such as K_2CO_3 was employed (*e.g.*, **25**, 54% (KOH), 86% (K_2CO_3)). Vinyl boronic ester (**31**) as well as alkyl boronic esters (**32–33**) were not only tolerated under our reaction conditions but showed superior stability towards decomposition than in classical organic solvents (decomposition of **33**: 25% (DMF), 5% (HPMC/water), see ESI, Fig. S5 and S6†). Furthermore, the synthesized boronic esters can be reacted in subsequent Suzuki–Miyaura couplings which enables easy derivatization necessary for example in medicinal chemistry for rapid structure–activity-relationship (SAR) generation. To showcase that this consecutive derivatization is possible using an aqueous reaction medium, we performed a two-steps one-pot synthesis by reacting 2-fluoro-5-cyanopyridine (**47**) with boronate **48** (see Scheme 3A). The resulting vinyl pinacol boronate **31** was used directly in a Suzuki–Miyaura coupling with bromobenzene and final product **50** was obtained in 77% yield over two steps.

To investigate other valuable precursors for subsequent modifications, brominated derivates **29** and **30** were synthesized. Remarkably, no elimination was observed for the aliphatic bromide **29**. Vinyl bromide **30** was further derivatized in a tandem Suzuki–Miyaura coupling, again, by reacting it in a one-pot procedure with phenylboronic acid to obtain coupling product **50** *via* this alternative route in 90% yield over two steps (see Scheme 3B).

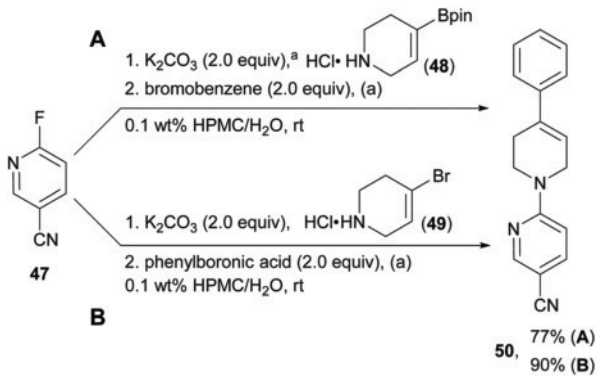
Further on, we discovered such functional groups as alcohols (**8**, **19–24**), carboxylic acids (**26**), or alkynes (**27**) which often require protecting groups to ensure chemoselectivity and prevent side reactions are well tolerated using HPMC/water as reaction medium. For instance, we observed a very high N- over O-selectivity for various aminoalcohols. In this course, we were able to synthesize a precursor for Dasatinib (**20**, Sprycel®), a tyrosinkinase inhibitor, without the formation of *O*-substituted or *N*,*O*-disubstituted by-products. Notably, the same clean reaction profile was observed for symmetrical 4-aminobutanol (**24**). For this reaction we were able to show that our methodology stands out from the classical reaction set-up in organic media where approx. 60% of the *N*,*O*-disubstituted product was observed (in contrast to 5% for the reaction in HPMC/water, see ESI, Fig. S7 and S8†). This circumvents the usage of protecting groups in several cases and thus leads to shortened reaction sequences and reduced use of potentially toxic chemicals required for introduction of these groups. Moreover, these functionalities enable consecutive modifications and reactions such as amide or Sonogashira couplings which can also be conducted in aqueous medium.[29,46] In addition to this excellent chemoselectivity, a remarkable regioselectivity was observed for the conversion of 2,4,5-trichloropyrimidine (**1**) as the 4-position was highly favoured (94 : 6 over the 2-position). This type of chemoselectivity cannot be achieved in organic solvents where a mixture of both regioisomers (69 : 31 over the 2-position, see ESI, Fig. S9 and S10†) is obtained.

Despite the superior selectivity and stability observed herein, general reactivity trends remained similar when using optimized reaction conditions in HPMC/water compared to organic solvents. For instance, reactions of electron deficient and therefore less nucleophilic amines resulted in low to moderate yields of the desired products (*e.g.* morpholine derivatives **17** and **22**, ketone **34**) and non-nucleophilic nitrogen groups such as carbamates, ureas, or amides showed no conversion (see ESI, Scheme S1†). This is also true for the reactivity of different electrophiles where we observed that either chloride or fluoride can be employed as leaving groups, with fluorides being more reactive. Moreover, substituent effects of electron withdrawing groups such as $-CF_3$, –CN, $-CO_2R$, –Cl, –Br, and $-NO_2$ were also comparable to those observed in organic solvents. However, suppression of hydrolysis for highly activated electrophiles such as 2-chloro-5-nitropyrimidine under aqueous basic reaction conditions remains an obstacle and resulted in low isolated yields of the desired products (see ESI, Scheme S2†). For less activated substrates it was observed that isolated yields increased upon heating to 50–60 °C (*e.g.* **15**: rt: 52%, 50 °C: 82%). This temperature dependency is also comparable to the behaviour in organic solvents; however, our method uses mild temperatures when compared to the ones that promote reactions in organic solvents (80–130 °C). These similarities in reactivities and operational principles will hopefully ease the transfer from organic solvents to reactions in an aqueous medium and reduce the reluctance of chemists to employ this more environmentally friendly methodology.

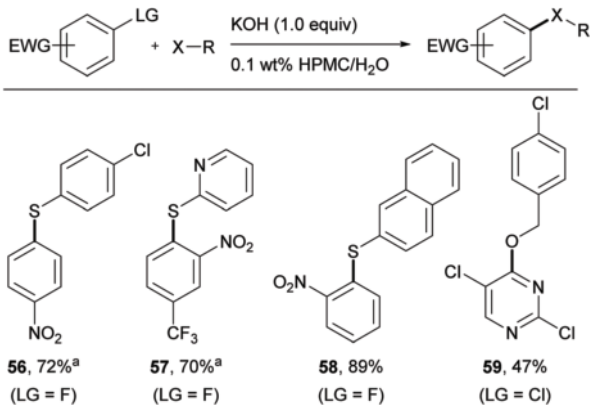
To further highlight the applicability of our methodology in medicinal chemistry, we reacted different five-membered heterocycles like oxazoles (**37**) and thiazoles (**38**) using our optimized conditions. The resulting products can be easily further derivatized by either ester hydrolysis or nitro group reduction followed by *e.g.* amide coupling. Therefore, these substituted five-membered heterocycles represent a valuable substance



Scheme 2 Substrate scope of the S_NAr reaction in HPMC/water using *N*-nucleophiles. All yields are reported as isolated yields. [a] HCl-salt of the corresponding amine was used, 2.0 equiv. base; [b] K_2CO_3 was used, [c] at 50 °C; [d] at 60 °C, 0.5 M; [e] 2.0 equiv. of the corresponding electrophile, 2.0 equiv. KOH.



Scheme 3 Tandem reactions of a one-pot S_NAr reaction followed by a Suzuki–Miyaura coupling starting either from the corresponding vinyl pinacol boronate **48** (A) or vinyl bromide **49** (B). Conditions: (a) $PdCl_2$(dtbpf) (0.02 equiv.), NEt_3 (3.0 equiv.), rt, 1 h. [a] K_2CO_3 was used to ensure stability of boronic ester moiety.

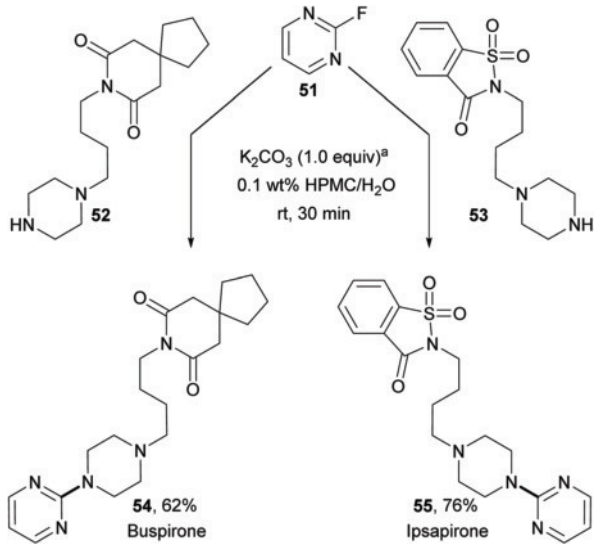


Scheme 5 Substrate scope of the S_NAr reaction in HPMC/water using *S*- and *O*-nucleophiles. [a] 60 °C, 0.5 M.

class for the pharmaceutical industry, which is not well covered in literature by now.

In addition, we were able to synthesize two distinct representatives of anxiolytic psychotropic drugs, Buspirone (**54**, Buspar®) by Bristol-Myers Squibb and Ipsapirone (**55**, see Scheme 4). Both products were obtained in good yields after only 30 min reaction time. Notably, the sensitive sulfonamide moiety of Ipsapirone was stable under aqueous basic reaction conditions. These reactions demonstrate the possibility to react more complex building blocks indicating the value of our methodology to the pharmaceutical industry.

To broaden the generality of our methodology we explored not only nitrogen-based nucleophiles but also *S*-nucleophiles and *O*-nucleophiles (see Scheme 5). Different thiols (**56–58**) were reacted successfully using the reaction procedure developed herein. Conversion of benzylic alcohol (**59**) was possible but interestingly, other *O*-nucleophiles were difficult to react under our standardized reaction conditions and need individual optimization in contrast to the other types of nucleophiles.



Scheme 4 S_NAr reaction towards two anxiolytic psychotropic drugs **54** and **55** in HPMC/water. [a] K_2CO_3 was used ensure stability of sulfonamide moiety of **53** and **55**.

Conclusions

We employed catalytic amounts of the benign polymer hydroxypropyl methylcellulose (HPMC) to enable nucleophilic aromatic substitution reactions in water using equimolar amounts of all reagents at mild temperatures. We applied these reaction conditions to the synthesis of a diverse substrate scope in which short reaction times, excellent chemo- and regioselectivities, as well as a broad functional group tolerance were observed. The latter allows further derivatization of the reaction products for the synthesis of biologically active compounds which are of interest to the pharmaceutical industry. We demonstrated scalability in which the usage of organic solvents was completely avoided throughout the whole reaction process as well as the application to the synthesis of APIs. Overall, we developed a general, efficient, and sustainable methodology that addresses several drawbacks associated with S_NAr reactions under classical reaction conditions.

Author contributions

All authors have given approval to the final version of the manuscript. Niginia Borlinghaus and Wilfried M. Braje are employees of AbbVie. Leon H. Braje was employee of AbbVie at the time of the study. Tharique N. Ansari, Deborah Ogulu, Sachin Handa, and Valentin Wittmann have nothing to disclose. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

Conflicts of interest

There are no conflicts to declare.

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