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Achieving Sustainability in Assembly of Modified Nucleosides Using Green Solvents

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Abstract:

Chemical modifications of nucleosides has been a topic of special interest for researchers given the plethora of applications these structural motifs have been able to demonstrate. For decades, such modifications have been performed in conventional volatile organic solvents that have severe environmental implications. Recent trend suggests a shift in the strategy with many researchers using sustainable and green solvents such as ionic liquids (ILs), H₂O, Deep Eutectic Solvents (DES) and 2-MeTHF for performing key transformations on the nucleoside structural motif. This review critically analyzes examples of nucleoside functionalization carried out in different sustainable solvents and also helps to assess the feasibility of such solvent choices for further applications.

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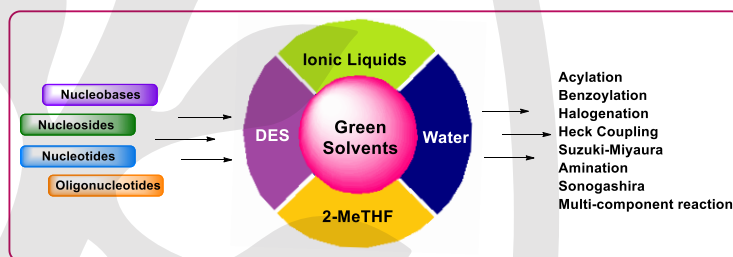
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SIGNIFICANCE (max 590 characters)

Nucleosides/nucleotides have become synonymous with a wide variety of anti-viral, anti-cancer agents as well as vaccines. Bringing sustainability in the synthetic processes in terms of the replacement of harmful volatile organic solvents with the environmentally benign sustainable solvents. This review comprehensively describes all such synthetic strategies for chemists in academia and industry to implement for long term benefits.



Keywords

Nucleosides, Sustainable Solvents, Green Solvents, Chemical Functionalization, Deep Eutectic Solvents, Ionic Liquids, Suzuki-Miyaura cross-coupling, Amination.

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ABSTR ACT

Chemical modifications of nucleosides has been a topic of special interest for researchers given the plethora of applications these structural motifs have been able to demonstrate. For decades, such modifications have been performed in conventional volatile organic solvents that have severe environmental implications. Recent trend suggests a shift in the strategy with many researchers using sustainable and green solvents such as ionic liquids (ILs), H₂O, Deep Eutectic Solvents (DES) and 2-MeTHF for performing key transformations on the nucleosides structural motif. This review critically analyzes examples of nucleoside functionalization carried out in different sustainable solvents and also helps to assess the feasibility of such solvent choices for further applications.

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1. Introduction

The past decade has seen an upsurge in the infections caused by viruses (COVID-19, Influenza, Dengue), and bacteria while cancer-related ailments have also risen exponentially.^{1–3} The scientific community has been constantly on the lookout for more potent drug candidates that can help tackle the pandemic-like situation that had arisen a few years back.⁴ A class of molecules that has emerged as a savior during the Covid-19 pandemic and will certainly define the treatment regimen for future situations are the chemically modified nucleosides (nucleotides).^{5–7} The introduction of mRNA vaccines during the pandemic proved to be a revolutionary scientific breakthrough leading to the saving of millions of lives and the eventual recognition of its future potential with a Nobel prize awarded to Kariko and Weissman for the application of base modified nucleosides in mRNA.^{8,9} Similar is the story with a growing number of broad-spectrum antivirals such as remdesivir, molnupiravir, favipiravir, etc. that were widely applied to contain the rapidly spreading Covid-19 pandemic.^{10–13} Post covid, nucleosides/nucleotide-based treatments have become common place as the first line of defense against viral infections and this field continues to grow at a fast pace.

With the growing requirement of nucleoside/nucleotide structural motifs for building the next level of ammunitions for tackling viruses or cancer, the development of sustainable synthetic methodologies for the construction of these molecules is necessary. Several reviews have recently been published discussing the various C—C, C—O, C—N, or C—X bond forming technologies for the modification of nucleosides with most protocols being performed in volatile organic solvents such as DMF, CH₃CN, THF, etc.^{14–19} This trend has been existed for many years but the environmental impact of these solvents are far reaching and pose a serious threat to not just the atmosphere but also led to the contamination of water bodies resulting into severe ecological impact.²⁰ Before the situation turns into a catastrophe, a definite push to promote a sustainable approach to the synthesis of nucleosides/nucleotides needs to be undertaken.

Use of sustainable or green solvents is one of the key principles of Green Chemistry as they can provide an alternative to the menace of volatile organic solvents. A large number of organic synthetic transformations over the years have been performed effectively in sustainable solvents such as H₂O, ionic liquids (ILs), deep eutectic solvents (DES), 2-MeTHF, glycerol, polyethylene glycol, and many more.^{21–24} Reviews focusing on each of these solvents separately have been published especially for general organic substrates rather than a very specific structural motif such as the nucleosides/nucleotides.^{25–32} Given the higher polarity, low vapour pressure, possible recyclable ability, and lower toxicity are the key contributors for the usage of sustainable solvents as a possible replacement of conventional organic solvents with most of the criteria fitting well for applying and achieving sustainability in the nucleoside/nucleotide modification.

There are reports in literature involving the use of some of these sustainable solvents in combination with conventional organic solvents with many of them already covered in the previously published reviews.^{33–36} In this review, selection of solvents are based on their compatibility with the principles of green chemistry, which include atom economy, non-toxic degradability, minimized environmental impact, and, in certain instances, natural sourcing. These solvents promoted sustainable, efficient, and eco-friendly processes without strict adherence to specific “green” criteria. This review will highlight literature examples involving the modification of

nucleosides/nucleotides in sustainable solvents such as ILs, H₂O, DES, and 2-MeTHF. Herein, a critical analysis of the literature offering the usefulness of the derived protocol and wherever necessary provide pointers to improve the conditions to achieve sustainability.

2. Ionic Liquids

ILs are essentially defined as organic salts that are liquids under ambient conditions preferably in the temperature range of 25–100°C.³⁷ Ionic liquids have come a long way since the first reported ionic liquid [EtNH₃][NO₃] by Walden³⁸ in 1914 that had a melting point of just 12°C.³⁹ The characteristic properties that make ILs so attractive are their highly polar nature providing the possibility of dissolution of a large variety of substrates as salts, having negligible vapor pressure and high boiling point which can be beneficial for performing reactions at high temperatures. ILs are also known to exhibit unique chemical and physical properties, such as non-volatility, non-flammability, non-miscibility with non-polar solvents, and reasonable thermal and chemical stability.^{40,41} Additionally, ILs are more sustainable for scale-up applications due to their recyclability, simple product isolation, catalyst immobilization, and improved reaction selectivity.^{42,43} To this date, these have been explored extensively as solvents in numerous reactions such as esterification reactions,^{44–46} cleavages of ethers,⁴⁷ aldol condensation,⁴⁸ protection of carbonyls,^{49–52} Koch carbonylation,⁵³ polymerization,⁵⁴ hydrogenation, regioselective alkylation, and Friedel-Crafts reactions,^{55–58} dimerization,^{59,60} Diels-Alder reactions,^{61,62} Mannich reaction,^{63,64} oximation and oxidation,^{65–67} Heck reaction,⁶⁸ Knoevenagel reaction,^{69–72} Henry reactions,⁷³ heterocyclic synthesis,^{74,75} cross-coupling reactions and some enzymatic reactions. Most of these processes have been performed on general organic substrates and only at the beginning of the 20th century that researchers started employing ionic liquids for the modification of nucleosides. Initially, ILs such as 1-butyl-3-methyl imidazolium tetrafluoroborate ([BMIM]BF₄), 1-Methyl-3-octyl-imidazolium-tetrafluoroborate ([OMI]BF₄), and 1-Butyl-3-methylimidazolium hexafluorophosphate ([BMIM]PF₆), were tested as additives in organic solvents for promoting synthetic nucleoside chemistry. During this period, several reports described the enhancement in the reaction rate and selectivity due to the addition of ILs.^{76–78} Encouraged by these findings, researchers subsequently started employing ILs as the sole solvent for the nucleoside modification processes. In this section, we summarize the published literature from last 20 years addressing the importance and utility of ILs in nucleoside chemistry. This section has been divided into two parts, first on the modification of the sugar moiety of nucleosides and the next on the modification or functionalization of the base moiety.

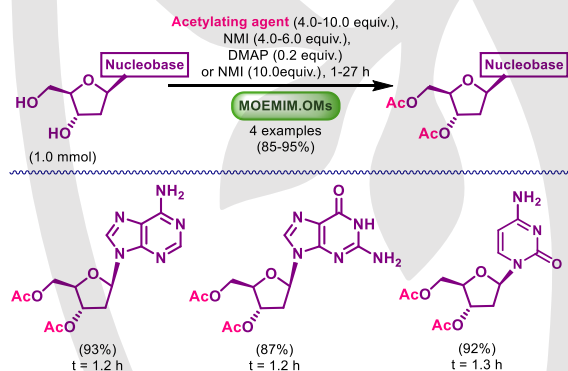
2.1 Modification of Sugar Moiety

The past decade has seen an upsurge in the number of nucleosides and their modified analogs that have been widely explored as antiviral and anticancer drugs.^{79,80} A typical nucleoside structural motif (bearing different base moieties linked to either ribose or 2'-deoxyribose sugar) bearing hydroxyl (sugar part) and amino groups (base part) that have similar chemical reactivities are needed to be

selectively protected as a part of the functionalization strategies.^{81,82} The selective protection/ deprotection of the hydroxyl group over the amino group is an important requirement in nucleoside chemistry and the employment of ILs as solvents for promoting these reactions has helped this issue effectively. Some of these protocols have been described in this section depending upon the type of protecting group to be installed.

2.1.1 Acetylation

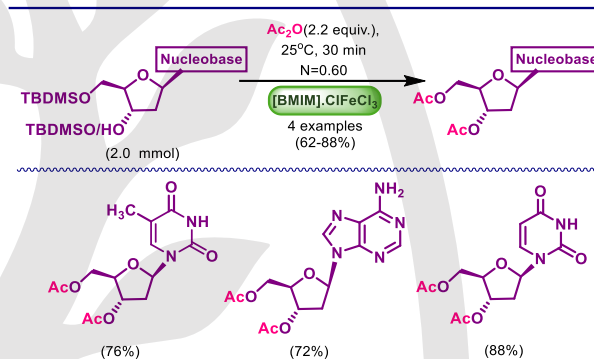
The most commonly employed protecting group for the sugar hydroxyl groups is the 'acetyl' functionality and these acetylated nucleosides have found common applicability as building blocks for the various synthetic nucleosides.⁸³⁻⁸⁵ The usefulness of acetylated nucleoside analogs stems from the fact that the non-acetylated bio-active nucleosides are known to exhibit susceptibility to the cleavage of the glycosyl bond (C–N) in the presence of nucleoside phosphorylase leading to the reduction of their biological activity.⁸⁶ In such cases, the acetyl derivatives (sugar hydroxyl protection) of these analogs have proven to be more efficient and are known to resist such transformations.^{87,88} For example, the improved anti-cancer activity exhibited by 3'-*O*-retinoyl-FUDR over the parent drug⁸⁹ further highlights the importance of acetyl functionality (sugar hydroxyl protection) and the development of sustainable synthetic protocols for their introduction into the nucleoside structural motif is of great interest to synthetic chemists.



Scheme 1 Acetylation of 2'-deoxyribonucleosides in MOEMIM.OMs.

ILs certainly have played a useful role in achieving this goal and some of these methodologies have been described below. One of the first examples for the use of ILs as a greener alternative to conventional organic solvents in nucleoside chemistry for the execution of the protection strategy (of sugar hydroxyls) was reported in 2003 by Salunkhe and co-workers⁸⁴ for the acetylation of nucleosides. An extensive array of ILs such as 1-butyl-3-methyl imidazolium chloride (BMIM.Cl), BMIM.BF₄, BMIM.PF₆, *N*-butyl pyridinium methanesulfonate (BPy.OMs), 1-ethyl-3-methyl imidazolium methanesulfonate (EMIM.OMs), 1-methoxyethyl-3-methyl imidazolium methanesulfonate (MOEMIM.OMs) were employed to first study the solubilities of different nucleosides. After comparing the solubilities of protected and unprotected 2'-deoxynucleosides with the

above-mentioned ILs with different organic solvents like pyridine, *N,N*-dimethylformamide (DMF), they chose MOEMIM.OMs as the solvent of choice for conducting further studies of acetyl protection of sugar hydroxyls. The authors further demonstrated the combination of (CH₃CO)₂O and (CH₃)₂COCl as acetylating agents, 1-methylimidazole (NMI) as the base, or in some cases, 4-*N,N*-dimethylaminopyridine (DMAP) was used in catalytic amount to promote the acetylation reaction effectively in MOEMIM.OMs ionic liquid (Scheme 1). Good yields of the bisacetylated 2'-deoxynucleosides was obtained using the above synthetic strategy. However, when authors tried to execute a selective acetylation strategy for the amine functionality (base part of the nucleoside) over the 3'- and 5'- hydroxy functional groups (sugar part) using a stoichiometric amount of Ac₂O they ended up with a mixture of products with no appreciable selectivity observed.



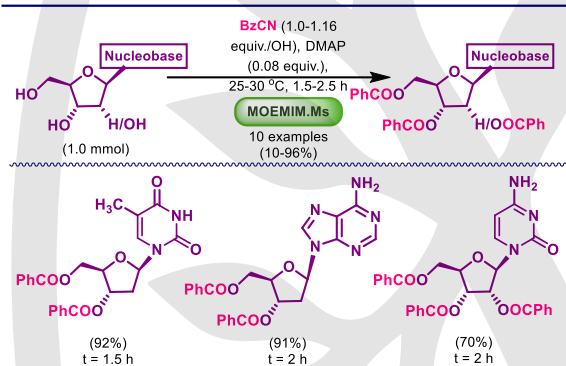
Scheme 2 Acetylation of silyl ether protected nucleosides in [BMIM]ClFeCl₃.

Building upon the success obtained with the employment of ILs for the execution of protection strategy on the nucleoside structural motifs, Salunkhe, and co-workers⁹⁰ in 2005 undertook another interesting acetylation strategy of nucleosides involving the transprotection of the previously silyl protected (3'-OH and 5'-OH groups of the sugar part) nucleoside. This was achieved by using a different IL than the one employed in the previous report i.e. 1-butyl-3-methylimidazolium chloride.FeCl₃ ([BMIM].Cl.FeCl₃) that had the ability to promote the deprotection of the silyl functionality in the presence of Ac₂O as the acetylating reagent yielding the diacetate-protected nucleoside as the product (Scheme 2). The Lewis acidic character of the IL was fine-tuned along with the reaction temperature to accelerate the desilylation most effectively in [BMIM].Cl.xFeCl₃. It is, therefore, ascertained by the authors that the IL [BMIM].Cl.FeCl₃ played the dual role of firstly acting as an efficient sustainable solvent and then further as a possible Lewis acid catalyst for promoting the deprotection of silyl and subsequent acetylation of the hydroxyl groups.

2.1.2. Benzoylation

As previously discussed, functionalized nucleosides have in the past decade brought about a revolution in the area of drug discovery, with themselves showing promising bioactivity and at the same time acting as useful building blocks for the synthesis of therapeutic oligonucleotides.⁹¹⁻⁹³ Multistep synthesis protocol for the rapid generation of bioactive nucleosides/nucleotides are marred with many problems out of which the selective

manipulation of hydroxyl and amino groups as discussed above is a major challenge.^{94,95} Acyl protection certainly is useful but the susceptibility of the acetate functionality towards hydrolysis makes it a less preferable protection strategy in a multistep synthetic model that can involve transformations that can prove to be detrimental to the acetate functionality.^{96,97} Benzoylation of the 3'-OH and 5'-OH groups (in case of 2'-deoxyribose) of the sugar part of the nucleosides certainly could prove to be an effective strategy for the selective protection of hydroxyl functionality in the presence of a competitive amino group in nucleosides/nucleotides.⁹⁸ Due to the improved stability of the benzoyl group, it is most commonly preferred over the acetyl group and in this part, we will be discussing about the various benzoylation protocols involving ionic liquids as the sole solvent to promote a sustainable protection methodology. Benzoylation has been performed most commonly using benzoyl chloride, which is a known lachrymator and alternative benzoylating reagents have therefore been explored in literature for the protection of -OH functionality either in aromatics or heteroaromatics.

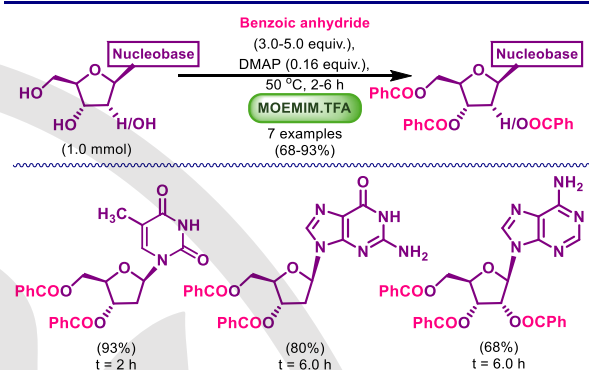


Scheme 3 Benzoylation of nucleosides using BzCN in MOEMIM.Ms.

Benzoyl cyanide as a benzoylating reagent is an interesting proposition and was first explored by Prasad, Parmar, and co-workers⁹⁹ who have reported a selective *O*-benzoylation (of the hydroxyl groups of the sugar part) over *N*-benzoylation (base part) of different nucleosides in MOEMIM.Ms ionic liquid (Scheme 3). Benzoylation using benzoyl cyanide was demonstrated to proceed effectively with a catalytic amount of DMAP for ribose as well as 2'-deoxyribose nucleosides. The authors predicted that the reason for benzoyl cyanide to be more selective than benzoyl chloride or benzoic anhydride towards favoring *O*-benzoylation over *N*-benzoylation was its comparatively lower reactivity. The role of the employed ionic liquid was also predicted to be promoting the selectivity due to its high polarizability allowing the hydroxyl group to be more nucleophilic than the amino group. The high solubility of nucleosides in MOEMIM.Ms also is a major contributor for achieving the highly efficient benzoylation protocol at ambient temperature and the reusability of the IL liquid further enhances its appeal as a solvent for such transformations.

The previous method for *O*-benzoylation of nucleosides in MOEMIM.Ms although showed high selectivity but taking into consideration a serious limitation about the possible evolution of HCN as a toxic by-product led the authors to explore benzoyl

anhydride as a useful alternative.



Scheme 4 Benzoylation of nucleosides using benzoic anhydride in MOEMIM.TFA.

Benzoyl cyanide reactivity was also observed to be in some cases not very encouraging and to circumvent this problem, in 2007, Kumar and co-workers¹⁰⁰ extended the study of *O*-benzoylation of nucleosides in ILs by the employment of benzoic anhydride as the benzoylating reagent. The reaction was performed in 1-methoxyethyl-3-methylimidazolium trifluoroacetate (MOEMIM.TFA) ionic liquids, however, the reaction temperature rather than being ambient temperature was increased to 50°C with DMAP added as a catalyst (Scheme 4). The authors observed that the MOEMIM.TFA performed better than other ionic liquids as well as conventional organic solvents and provided improved solubility as well as selectivity in the benzoylation of hydroxyl groups of both 2'-deoxyribose and ribonucleosides. The risk of HCN was also mitigated well using benzoic anhydride, however, it is important to note that the compound is a lachrymator, and one needs to be careful in working with benzoic anhydride too. An important advantage of using the MOEMIM.TFA ionic liquid was the recyclability (3 cycles) achieved using this medium which is not possible under the conventional reaction conditions. Fewer number of examples pertaining to the modification of the sugar moiety of nucleosides in ILs suggests that the reactions beyond selective protection of hydroxyl groups nothing yet has been explored and there is certainly scope to develop efficient protocols for sugar modification.

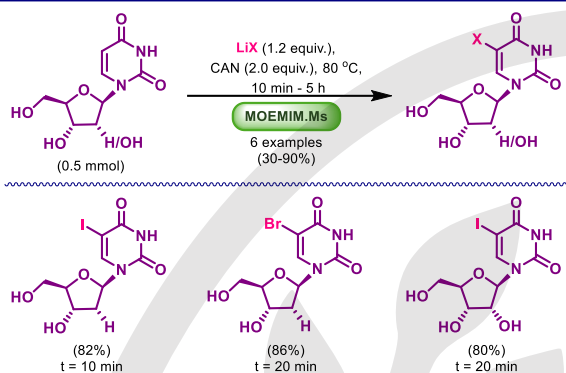
2.2 Modification of Nucleobases and Nucleoside

In the preceding section we focused on the examples involving base modification (nucleobase) in the nucleosides. As most of these reactions have been performed in conventional organic solvents, the attractiveness of using a sustainable solvent such as an ILs would be related to better solubility of the polar nucleosides, improved reactivity, better product separation, and possible recycling of the reaction solution. Herein, we describe such transformations that have been performed primarily in ILs specifically targeting the nucleobase modification.

2.2.1 Halogenation

Halogenation of aromatics and heteroaromatic moieties is one of the most applied and useful synthetic transformation in synthetic

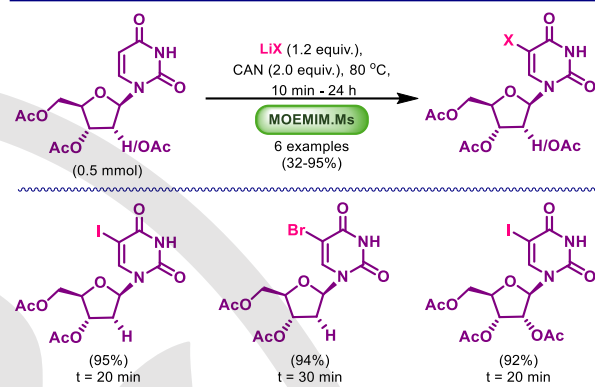
organic chemistry helping to create a useful handle (C—X) for further manipulation.^{101–103}



Scheme 5 Synthesis of 5-halouridines and 5-halo-2'-deoxyuridines in MOEMIM.Ms.

Selective halogenation of (hetero)aromatic compounds especially, nucleobases has been an extensively studied topic utilizing conventional organic solvents in combination with a wide variety of halogenating reagents. Previously reported methods for halogenation have many disadvantages like the use of toxic oxidizing agents or catalysts (HNO_3 , H_2SO_4 , sodium azide, etc.) and high boiling point solvents (DMSO, DMF, pyridine, acetic acid, etc.) leading to the contamination of the desired product. These methodologies are also known to suffer from poor selectivity, reduced reactivity, difficulty in isolation as well as the common problems of environmental pollution caused due to the usage of volatile solvents.^{18,103,104} Ionic liquids can provide a sustainable solution to these issues in halogenation reactions.

The importance of halogenation of nucleosides stems from the usefulness of some of these analogs as potent anti-cancer or anti-viral drugs. 5-Fluoro-2'-deoxyuridine (flouxuridine) and 5-iodo-2'-deoxyuridine (idoxuridine) are known potent anti-cancer and anti-viral drugs, respectively known for their highly effective bioactivities while the other 5-halouridine nucleosides have also been explored as anti-neoplastic agents and in recent years as fluorescent probes for studying DNA metabolism.^{18,105–107} Halogenation of the C5 position of uridine (ribose or deoxyribose nucleoside) therefore, becomes a synthetically useful methodology and in 2009, Kumar, Malhotra, and co-workers¹⁰⁸ reported the first synthesis of 5-halouridine in ionic liquid as a sustainable solvent (Scheme 5). For carrying out the halogenation of uridine nucleobase, authors performed the reaction using LiX as the halogenating agent with ceric ammonium nitrate (CAN) as the oxidizing agent at 80 °C in MOEMIM.Ms as the suitable solvent.

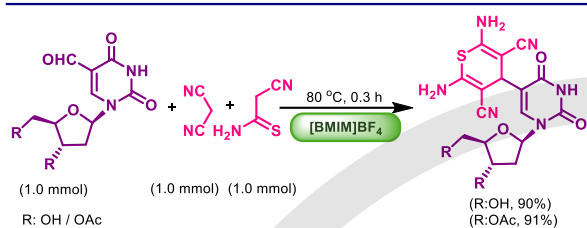


Scheme 6 Synthesis of acetylated derivatives of 5-halouridines and 5-halo-2'-deoxyuridines in MOEMIM.Ms.

Rapid conversions were observed for some of the nucleobases (10–20 minutes) and the conditions were found to be equally suitable for 2'-deoxyribose and ribonucleosides. Selective halogenation of unprotected nucleosides is certainly of interest as further manipulation of the sugar moiety could be made possible for further applications however, halogenation of protected nucleosides is equally important which was achieved effectively by the authors using the developed protocol (Scheme 6). The protocol was found to work equally well on the protected uridine or deoxyribose uridine. The developed method in comparison to the previously reported ones has emerged as an effective greener alternative due to the following factors: negligible vapor pressure of ILs, recyclability, high thermal stability, high solubility of nucleosides in ILs, and easy workup for the isolation of the desired product.

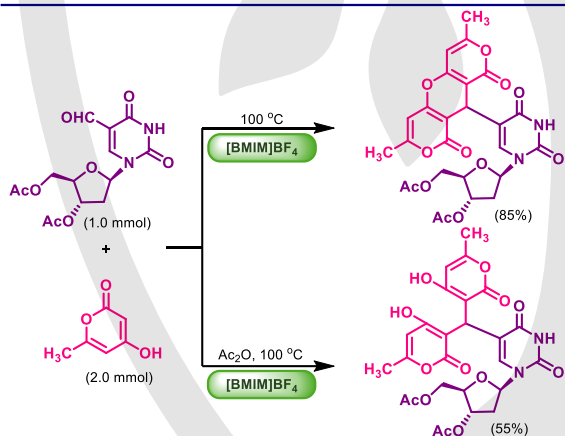
2.2.2. Multicomponent Reactions

A multicomponent synthetic transformation involves the combination of two different substrates under uncatalyzed or catalyzed conditions to furnish the desired product. Complexity can be increased many folds by the incorporation of more than 2 substrates in a single pot procedure to form products. Multicomponent reactions (MCRs) as they are called nowadays have been known in literature for decades and have become a corner-stone of organic chemical processes.^{109,110} MCRs have been applied extensively to general organic substrates to build complex synthetic molecules which have exhibited promising biological activities.^{111,112} However, functionalization of nucleosides is a difficult proposition due to the lower solubilities of these substrates in organic solvents. This leads to poor yields and tedious work-up procedures while the environmental impact of using volatile organic solvents certainly outweigh most other problems.^{113–115} In this part, MCRs performed on nucleosides in ionic liquids is discussed.



Scheme 7 Multicomponent synthesis of pyrimidine nucleoside-thiopyran hybrids in [BMIM]BF₄.

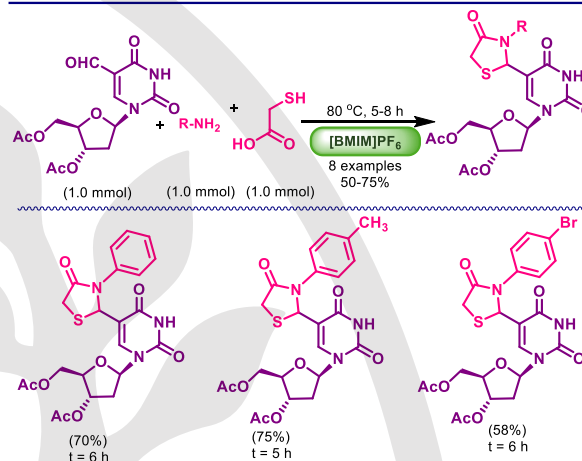
Thiopyrans have been extensively used for the synthesis of biologically important derivatives of natural products such as tetrahydrocannabinone,^{116,117} serricornin,¹¹⁸ thromboxanes,^{119,120} and cyclopentanoids.¹²¹ Fan, Qu, and co-workers¹²² have contributed extensively in the field of multicomponent reactions and in 2008, they reported a one-pot multicomponent synthesis of pyrimidine nucleoside-thiopyran hybrids in an ionic liquid [BMIM]BF₄. The authors demonstrated a [BMIM]BF₄-mediated reaction of 5-carbaldehyde-2'-deoxyuridine, cyanothioacetamide, and malononitrile to yield thiopyran derivative at 80 °C without any added catalyst (Scheme 7). On comparison with the conventional organic solvents (previously reported literature), [BMIM]BF₄ as an ionic liquid proved to be better in providing a protocol that requires mild reaction conditions, provides good selectivity and better yield as well as allows reusability of the reaction solution up to 5 reaction cycles. Accelerated reaction rates were also observed with the use of [BMIM]BF₄ as it promotes the MCR to be performed under shortened reaction time (within 0.3 h) compared to the reactions carried out in several conventional volatile organic solvents, such as methanol, ethanol, benzene, and THF (4-12 h).



Scheme 8 Synthesis of 5-substituted pyrimidine nucleoside derivatives in [BMIM]BF₄.

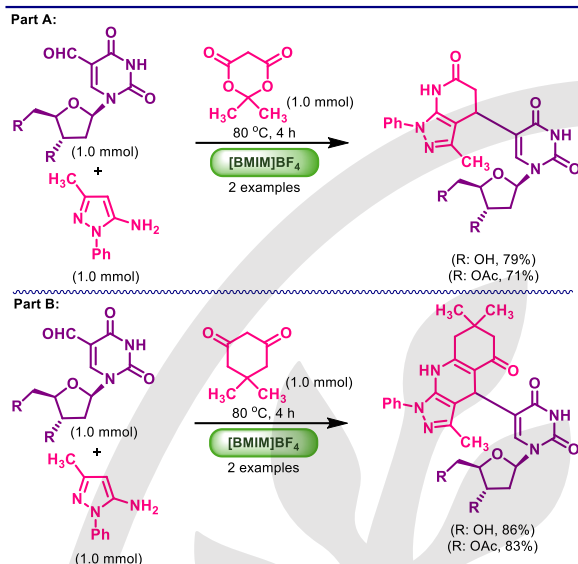
Building upon the success of employing the sustainable ionic liquids for the nucleoside modifications, Fan, Zhang, and co-workers¹²³ further decided to functionalize the 5-carbaldehyde-2'-deoxyuridine (protected) with 2-pyranone (2 molecules) using a multicomponent approach. This methodology was based on the literature reports on pyran and its derivatives that are known to show promising cytotoxic and anti-tumor properties. The transformation involved the synthesis of 2'-deoxyuridine nucleoside-fused pyran derivatives by the reaction of 5-

carbaldehyde-2-deoxyuridine and 4-hydroxy-6-methyl-2-*H*-pyran-2-one in [BMIM]BF₄. In the presence of Ac₂O at 100 °C. The products, 2'-deoxyuridine nucleoside-bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl) methane hybrids were predicted to show promising bioactivity while the novel process thus developed exhibits high efficiency in a sustainable ionic liquid.



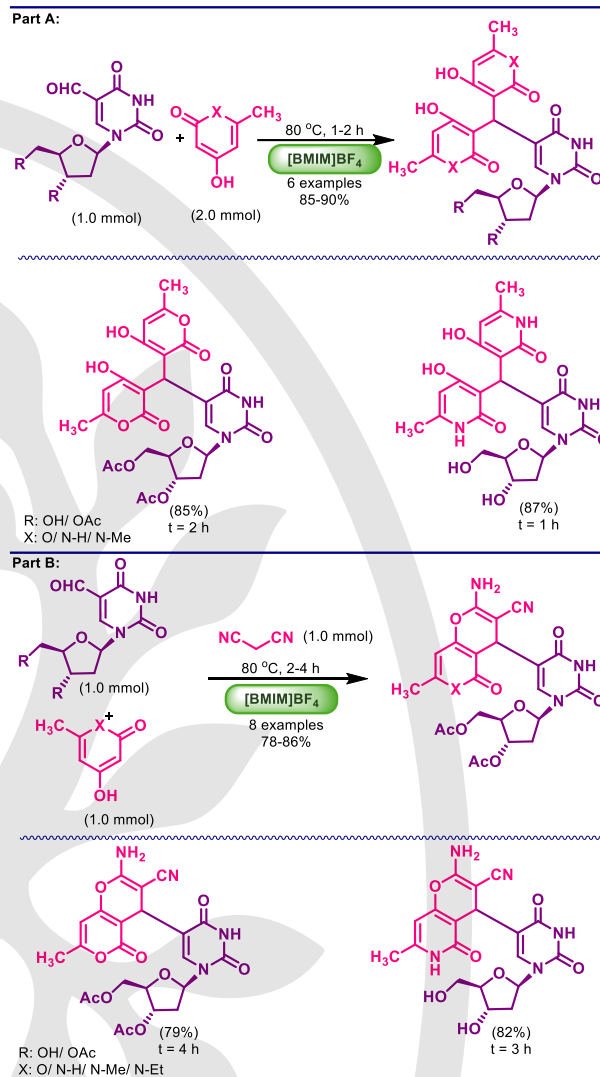
Scheme 9 Synthesis of pyrimidine nucleoside-thiazolidinone hybrids in [BMIM]PF₆.

Another moiety that has found wide spread utility due to its promising biological activities such as anti-inflammatory,¹²⁴ antiproliferative,^{125,126} anticyclooxygenases (COX-1 and COX-2),^{127,128} anti-histaminic,¹²⁹ and anti-bacterial¹³⁰ activities is the thiazolidinone and its derivatives. Combining thiazolidinone structural feature with nucleosides could certainly help enhance the bioactivity further. Going with this idea, Fan, Qu, and co-workers¹³¹ further expanded their methodology of utilizing ILs as solvents and promoters for carrying out MCRs on nucleosides, developed in 2009 an ionic liquid-mediated one-pot multicomponent synthesis of 2'-deoxyuridine nucleoside-thiazolidinone hybrids (Scheme 8). The one-pot MCR was executed on 5-carbaldehyde-2'-deoxyuridine as the aldehyde coupling partner, with mercaptoacetic acid and corresponding amine as the other reactants in [BMIM]PF₆ at 80 °C. The developed protocol provided good to moderate yields of the desired hybrids in a shorter reaction time compared to the other conventional organic solvents like EtOH, THF, PhMe, CH₂Cl₂, etc. The authors also demonstrated the successful recovery and reuse of [BMIM]PF₆ without any significant loss in activity. The synthesized hybrids were subjected to bioactivity analysis against trypanomastigote forms of *T. brucei brucei* showing moderate activity.



Scheme 10 Part A: Synthesis of pyrimidine nucleoside-pyrazolo[3,4-b]pyridine hybrids in [BMIM]BF₄. **Part B:** Synthesis of pyrazolo[3,4-b]quinolinone hybrids in [BMIM]BF₄.

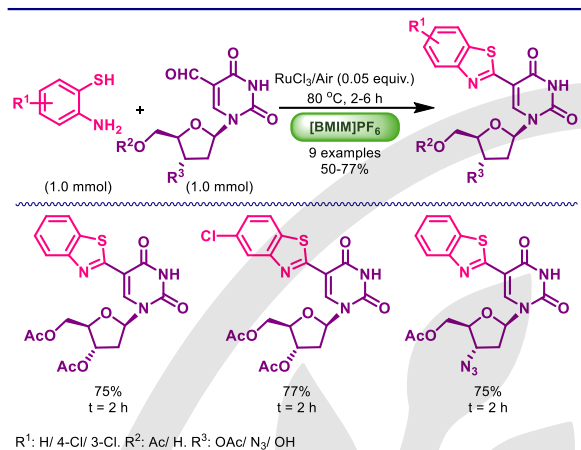
Another moiety that has attracted the attention of researchers because of their promising bioactivity are the pyrazolo[3,4-b]pyridines derivatives which have found relevance in studies pertaining to the identification of potent psychotropic,¹³² cytotoxic,¹³³ anti-viral,¹³⁴ anti-fungal,¹³⁵ and anti-chagastic agents.¹³⁶ Introducing such a useful structural motif on the nucleoside backbone will certainly enhance the bioactivity further and keeping this in mind, in 2009, Zhang and co-workers¹³⁷ demonstrated a novel one-pot multicomponent synthesis of 2'-deoxyuridine-pyrazolo[3,4-b]pyridin-6-one and 2'-deoxyuridine-pyrazolo[3,4-b]quinolinone hybrids. For achieving the synthesis of these hybrids, authors carried out a one-pot multicomponent reaction involving 5-amino-3-methyl-1-phenylpyrazole, Meldrum's acid, and 5-carbaldehyde-2'-deoxyuridine in [BMIM]BF₄ as the ionic liquid at 80 °C yielding 2'-deoxyuridine-pyrazolo[3,4-b]pyridin-6-one hybrids (Part A, Scheme 10). To achieve the synthesis of 2'-deoxyuridine-pyrazolo[3,4-b]quinolinone hybrids a slight modification in the protocol was undertaken by the authors by using 5,5-dimethyl-1,3-cyclohexadione instead of Meldrum's acid (Part B, Scheme 10). A comparison with the protocols developed in conventional organic solvents like THF, EtOH, and PhMe suggest that the ionic liquid, [BMIM]BF₄ provided improved product yield. The process also provides several advantages such as the reusability of solvent, high efficiency, simple procedure, and the environmentally benign nature of the solvent.



Scheme 11 Part A: Synthesis of pyridinone or pyranone nucleoside hybrids in [BMIM]BF₄. **Part B:** Synthesis of pyrano[3,2-c]pyridone, pyrano[4,3-b]pyran hybrids in [BMIM]BF₄.

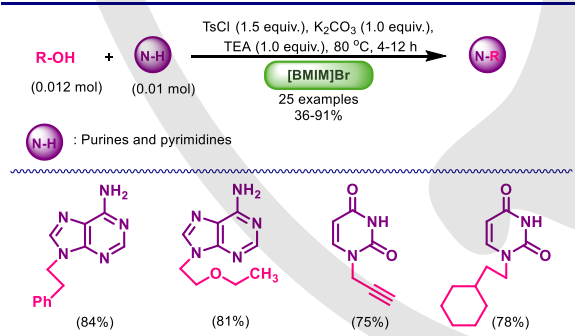
In continuation of the successful use of ionic liquids for the functionalization of nucleosides, Fan and co-workers¹³⁸ in 2010 demonstrated the synthesis of pyrano[3,2-c]pyridine as well as pyrano[4,3-b]pyran hybrids. The transformation was carried out by performing a one-pot reaction of 5-formyl-2'-deoxyuridine and heterocyclic derivatives in an ionic liquid, [BMIM]BF₄ at 80 °C to afford 2'-deoxyuridine nucleoside functionalized at the C5 position with pyridin-2(1H)-one or 2-pyranone (Part A, Scheme 11). They went on to also report a similar synthesis of 2'-deoxyuridine nucleoside functionalized with pyrano[3,2-c]pyridine moiety in the presence of malononitrile (Part B, Scheme 11). The use of [BMIM]BF₄ played a crucial role in promoting the reactivity of these transformations providing better yields compared to the conventional organic solvents. Higher polarity and ability of IL to solubilize both organic and inorganic components essentially help enhance the rate and selectivity of reactions.

2.2.3. Miscellaneous Reactions in Ionic Liquids



Scheme 12 Synthesis of pyrimidine nucleoside-benzothiazole hybrids in [BMIM]PF₆.

2-Substituted benzothiazoles are important synthetic compounds that have been investigated extensively for their pharmacological and biological activities such as antitumor, antiviral, antimicrobial, and antioxidant agents.^{139,140} Synthetic methodologies for the preparation of 2-substituted benzothiazoles are numerous ranging from cross-coupling, C—H bond functionalization, etc.^{141,142} Introduction of benzothiazole moiety on the nucleoside backbone can give rise to biologically useful derivatives which can also exhibit promising fluorescent activity.^{143,144} Coupling reactions especially, Suzuki-Miyaura coupling has been used for the incorporation of the benzothiazolyl functionality on nucleosides especially, 2'-deoxyuridine at the C5 position of the base. Other strategies have also been known but most have been performed in volatile organic solvents. In 2010, Fan and co-workers¹⁴⁵ illustrated a Ru(III)-catalyzed oxidative reaction in ionic liquid. The authors performed the reaction of 5-formyl-2'-deoxyuridine nucleoside and *o*-aminobenzenethiol in the presence of RuCl₃/[BMIM]PF₆ at 80 °C to yield 5-benzothiazolyl substituted 2'-deoxyuridine nucleoside hybrids (Scheme 12). The reaction proceeded with good to moderate yields of the desired product and the reaction was governed by the key role of [BMIM]PF₆ to not only act as a solvent or a co-catalyst but also in helping to immobilize the Ru-catalyst thus enabling the recycling of the catalytic solution.



Scheme 13 *N*-alkylation of nucleobases using alcohols in [BMIM]Br.

N-Alkylation of heteroarenes is an important synthetic strategy especially applied to nucleosides due to the significance of acyclic nucleosides is on the rise due to their enhanced stability

compared to the cyclic nucleosides and the promising activity as pharmaceutical agents for viral and cancer chemotherapy further contributes favourably for acyclic nucleosides.^{146–148} Numerous *N*-alkylation protocols are known but none have been conducted in sustainable solvents such as ILs. In 2015, Rad and co-workers¹⁴⁹ reported a one-pot *N*-alkylation of nucleobases with alcohols as the alkylating agents using a reagent combination of TsCl/K₂CO₃/TEA in 1-butyl-3-methylimidazolium bromide ([BMIM]Br) (Scheme 13). The methodology was performed on purines, pyrimidines, andazole derivatives. Primary or secondary alcohols were to provide good to excellent yields of the desired *N*-alkylated product while tert-alcohols were found to be unsuitable for the given transformation. The developed process has been observed to be highly efficient, safe, and environmentally compatible as the use of toxic and hazardous materials such as DMF and alkyl halides has been prevented.

3. Water

Synthesis of structural analogs of naturally occurring nucleosides is challenging due to their physicochemical and structural properties. The poor solubility of nucleosides in organic solvents, the presence of multiple functionalities, and acid sensitivity towards hydrolytic cleavage of glycosidic bonds make the synthesis more complicated.¹⁵⁰ To carry out the synthesis of modified nucleosides in organic solvents, fully protected nucleoside analogs have commonly been employed. However, organic solvents often get contaminated with the desired product due to difficulties in their isolation. Although, ILs have been widely explored as sustainable solvents^{41,151} for their advantages, ILs could sometimes cause corrosion and may react with other chemicals in the reaction mixture. Furthermore, ILs could also get contaminated by moisture in the environment as well as other gases on exposure. Synthesis of ILs is often challenging¹⁵² and the products pose potential environmental impact throughout their life cycle.^{153–156} Therefore, much attention has been drawn to water as a possible greener solution. A mixture of organic solvents with water has also been tried for developing the synthetic methodologies for various unprotected nucleosides as the combination can help facilitate the solubility of these substrates.^{35,96,157,158} However, performing nucleoside functionalization reactions in water as a sole solvent is a demanding proposition as the solubility of the nucleosides is not the only criteria but the compatibility of the various reagents also plays an important role. In recent years, several researchers have reported cross-coupling reactions of nucleosides in aqueous media especially, Suzuki-Miyaura coupling for the synthesis of fluorescent nucleosides. This section summarizes the methodologies that have been performed solely in water as the green solvent.

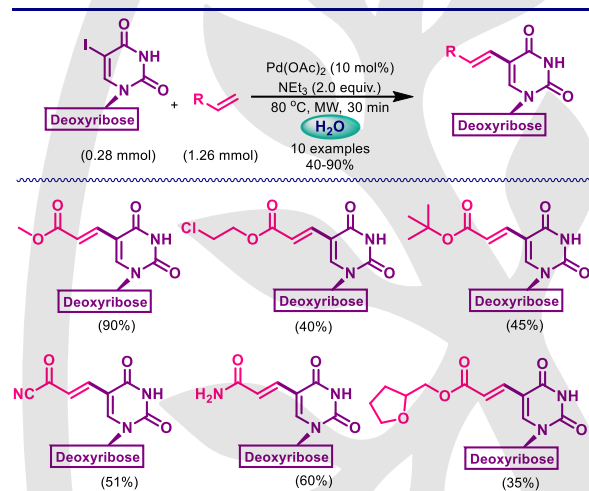
3.1 Modification of Nucleobases and Nucleosides

The modification of the sugar part of the nucleosides is more limited to protection strategies while the base moiety provides more opportunities to install functional groups using a range of metal-mediated or metal-free synthetic methodologies. In our discussion, we excluded the protocols where a combination of

solvents has been employed with water. What follows are the procedures using water as primary solvent.

3.1.1. Heck Coupling

Heck reaction is a common strategy employed by researchers for C—C bond formation to construct useful derivatives of agrochemicals, fine chemicals, and pharmaceuticals.^{159,160} The first reaction was documented by Mizoroki¹⁶¹ in 1971 and Heck¹⁶² in 1972. Since then, this reaction has been extensively explored due to its high efficiency, simplicity, high chemoselectivity, mild reaction conditions, low toxicity, and low cost.^{163–165} To expand the scope of the reaction and to make the catalytic process environmentally benign, tremendous efforts have been taken by researchers to study these reactions in various green solvents such as water.



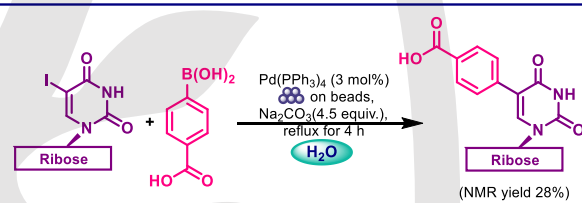
Scheme 14 Heck coupling of 5-iodo-2'-deoxyuridine with acrylate derivatives in water.

Literature reports suggest that the structural modification of nucleosides with different functionalities especially alkenes have shown significant enhancement in their chemotherapeutic potential. In 2014, Herve and Len¹⁶⁶ made the first effort in the synthesis of modified nucleoside in aqueous media via the Heck alkenylation reaction that has been commonly used for the introduction of alkenyl functionalities on various substrates. The authors reported a ligand-free, microwave-assisted Heck cross-coupling reaction of nucleoside in neat water. The reaction was performed on 5-iodo-2'-deoxyuridine with various acrylate derivatives in the presence of Pd(OAc)₂ as a catalyst without the addition of any ligand, NEt₃ as the base in pure water at 80 °C under microwave conditions (Scheme 14). Several examples of derivatized nucleosides were obtained in good to excellent yields. Besides these examples, authors have also put forth a greener route for the synthesis of 2'-deoxyuridine-5-carboxylic acid (CVU) and anti HSV-1 inhibitor, BVDU providing 80% and 56% yields of the respective products.

3.1.2. Suzuki-Miyaura Cross-Coupling

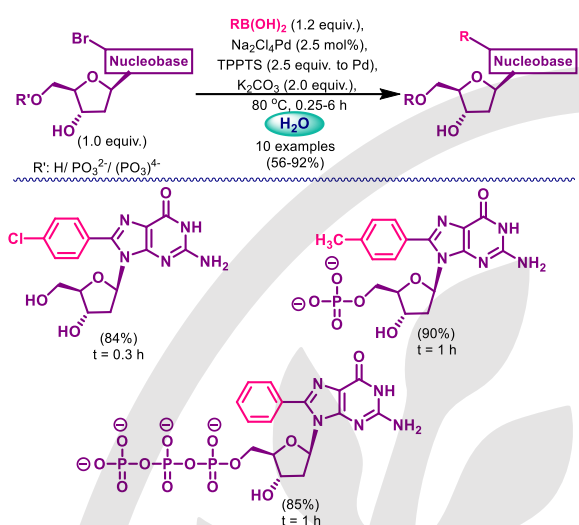
Suzuki-Miyaura coupling is the most applicable and useful C—C bond forming technologies allowing the cross-coupling

reactions between the aryl or vinyl boron-based (boronic acids, boronate esters) reagents with aryl or vinyl halides catalyzed by a wide variety of Pd-complexes.^{167–169} Although cross-coupling reactions like the Heck reaction, Stille reaction, and others also offer similar outcomes for C—C coupling, this reaction has been the most prevalent methodology due to the amazingly milder reaction conditions of the developed protocols, commercial availability of a diverse range of boron reagents, less toxic nature of the boron reagents compared to other organometallic reagents, excellent functional group tolerance, and operational simplicity. For the synthesis of structural constituents of numerous agrochemicals, natural products, pharmaceuticals, and polymers, the Suzuki-Miyaura reaction has been widely explored.^{170–172} In the modification of nucleosides too, Suzuki-Miyaura cross-coupling has also played an important role with several research groups reporting coupling reactions in volatile organic solvents (DMF or CH₃CN) or a combination of an organic solvent with H₂O (DMF:H₂O or CH₃CN:H₂O).^{35,173} The use of water as a sole solvent for Suzuki-Miyaura cross-coupling of nucleosides would be a desirable option given the greener appeal of H₂O. This section provides an overview of what has been achieved till date on promoting Suzuki-Miyaura in water using Pd-catalytic system.



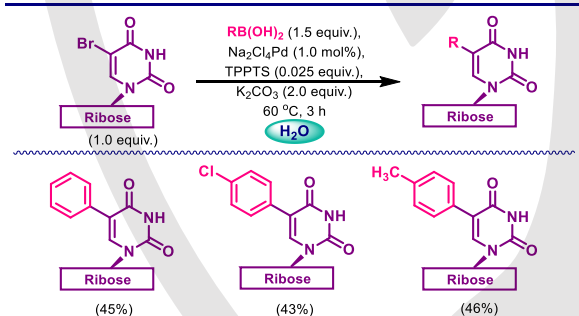
Scheme 15 Suzuki-Miyaura cross-coupling reaction of 5-iodouridine with arylboronic acid.

One of the earliest examples of performing Suzuki-Miyaura cross-coupling of nucleosides in water was reported in 2003 by Williams and co-workers¹⁷⁴ who developed a Suzuki-Miyaura coupling protocol that involved the use of reverse-phase glass beads in combination with Pd(PPh₃)₄ wherein the Pd-catalyst could be said to be immobilized on the glass beads surface. The catalytic system thus derived was further utilized for the functionalization of 5-iodouridine using 4-carboxyphenyl boronic acid via Suzuki cross-coupling (Scheme 15). As a part of the catalytic protocol, authors used 3.0 mol% of Pd(PPh₃)₄-derivatized glass beads in the presence of Na₂CO₃ under refluxing condition using water as a solvent. It is important to note that the formation of a product during the reaction was determined by subjecting the crude reaction mixture to NMR analysis suggesting 28% product formation.



Scheme 16 Suzuki–Miyaura coupling of 8-bromoguanosine with arylboronic acid.

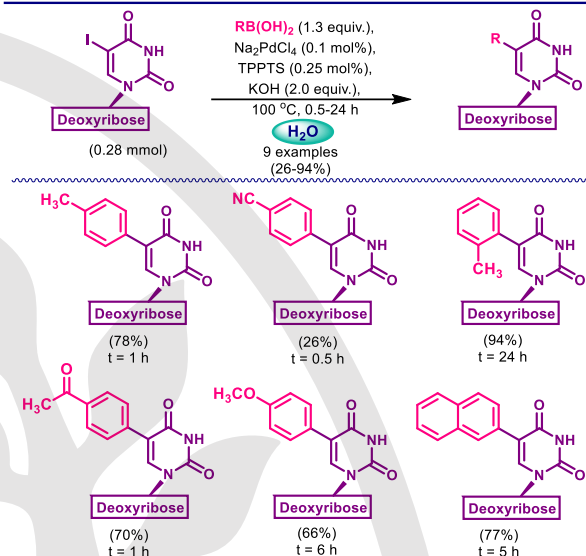
Collier and Wagner¹⁷⁵, in 2006, worked on the functionalization of 8-bromoguanosine using arylboronic acids via Suzuki–Miyaura coupling in water. The authors optimized the catalytic conditions and observed that $\text{Na}_2\text{PdCl}_4/\text{TPPTS}$ (triphenylphosphine trisulfonic acid) catalytic system was more effective in catalyzing the transformation compared to $\text{Pd}(\text{NO}_3)_2/\text{TPPTS}$ while it also being a low-cost option as well as more stable (Scheme 16). The Suzuki–Miyaura coupling protocol was performed at 80 °C in water as the only solvent with the desired products obtained in good to moderate yield. Effectiveness of the developed protocol allowed the authors to use the optimized conditions for the challenging coupling of 8-bromoguanosine monophosphate and 8-bromoguanosine triphosphate with different arylboronic acids affording the coupled products in good to moderate yields in competitive reaction times.



Scheme 17 Suzuki–Miyaura cross-coupling reaction of 5-iodouridine with arylboronic acid.

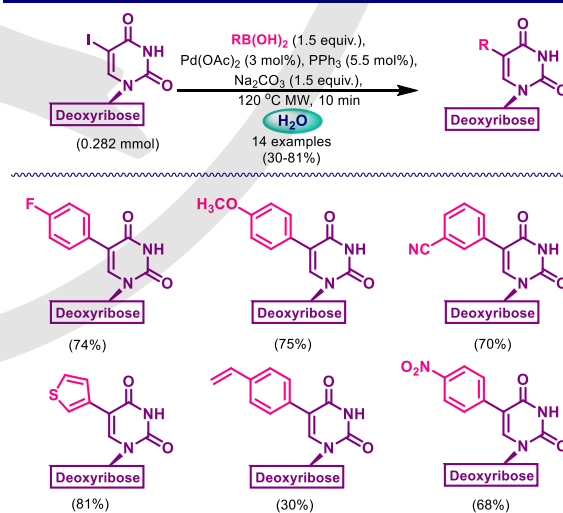
Wagner and co-workers¹⁷⁶ continuing on their previous work reported synthesis of fluorescent analogues of uridine diphosphate-ribose derivatives (Scheme 17). To achieve these target molecules, they developed a synthetic route that involved the functionalization of 5-iodouridine via Suzuki–Miyaura cross-coupling in an aqueous medium. 5-Iodouridine was reacted with arylboronic acid in the presence of $\text{Na}_2\text{PdCl}_4/\text{TPPTS}$ as the catalytic system, K_2CO_3 as the base, in water at 60 °C for 3.0 h. Although the reaction proceeds in water, product yields

reported have been low to moderate yield suggesting the less effectiveness of the developed catalytic system.



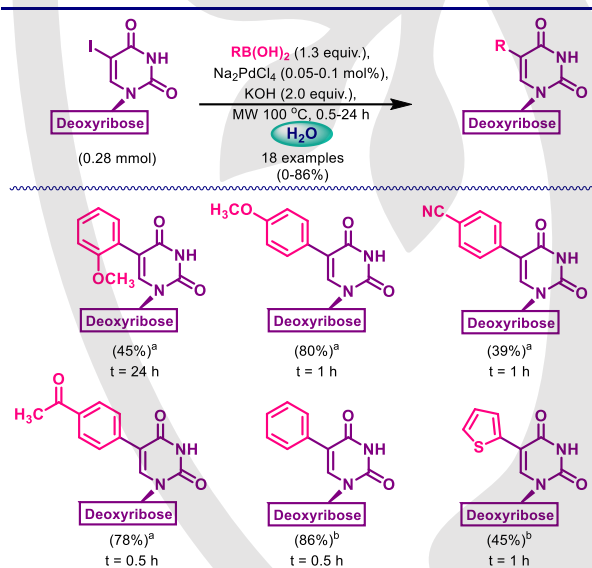
Scheme 18 Suzuki–Miyaura coupling of 5-iodouridine with arylboronic acid in water.

Early examples were focused towards the functionalization of ribose nucleosides in water but given the significance of deoxyribose nucleosides in the development of DNA-based functional probes and the related study, the contribution by Len and co-workers¹⁷⁷ in 2012 for demonstrating the synthesis of 5-substituted 2'-deoxyuridine analogs using Suzuki–Miyaura cross-coupling in water needs special mention. Water as a reaction solvent was chosen over other organic solvents because of its non-toxic nature, ready availability, and being environmentally benign. The catalytic system selected by Len and co-workers was the same previously used by Wagner and co-workers, i.e. $\text{Na}_2\text{PdCl}_4/\text{TPPTS}$. Using the preformed catalyst in water, Len and co-workers synthesized the derivatized 5-substituted 2'-deoxyuridine analogs in the presence of KOH as the base in water at 100 °C (Scheme 18). Improved reactivity for the developed catalytic system was attributed to the solubility of 5-iodonucleoside, arylboronic acid, and the inorganic base in water while the catalyst also is solubilized as TPPTS is a water-soluble ligand coordinating strongly with the Pd-centre.



Scheme 19 Suzuki–Miyaura coupling of 5-iodo-2'-deoxyuridine with arylboronic acid in water.

Compared to the previously reported literature, this method is superior due to the low catalyst loading achieved and greener for use of water as sole solvents instead of a mixture of water with organic solvents (H₂O/THF/MeOH, H₂O/MeCN or H₂O/MeOH). They have reported good to moderate yields of the desired product. Several parameters are essential to be considered for the modification of nucleosides as these are in general acid and temperature labile due to the readily dissociable glycosidic C–N bond. Reaction time can also play a crucial role to avoid the formation of any undesired byproduct during the coupling process. Berteina-Raboin and co-workers¹⁷⁸ in 2012 accordingly described the synthesis of 5-substituted-2'-deoxyuridine derivatives via Suzuki–Miyaura reaction in aqueous media under microwave conditions at 120°C with the reaction proceeding smoothly in just 10 minutes (Scheme 19). During the optimization of the synthetic protocol, authors had started with a mixture of water and acetonitrile as solvent and achieved 62% yield of the desired product. Further switch to only an aqueous medium improved the product yield albeit only slightly but they demonstrated that organic solvent such as CH₃CN could be completely avoided. The catalytic reactions were thus carried out in water as a sole solvent by the addition of Pd(OAc)₂ (3.0 mol%) as the catalyst, PPh₃ (5.5 mol%) as ligand, and Na₂CO₃ (1.5 equiv.) as the base at 80°C under microwave conditions to rapidly convert 5-iodo-2'-deoxyuridine into the respective derivatized products in good yields with different arylboronic acids.

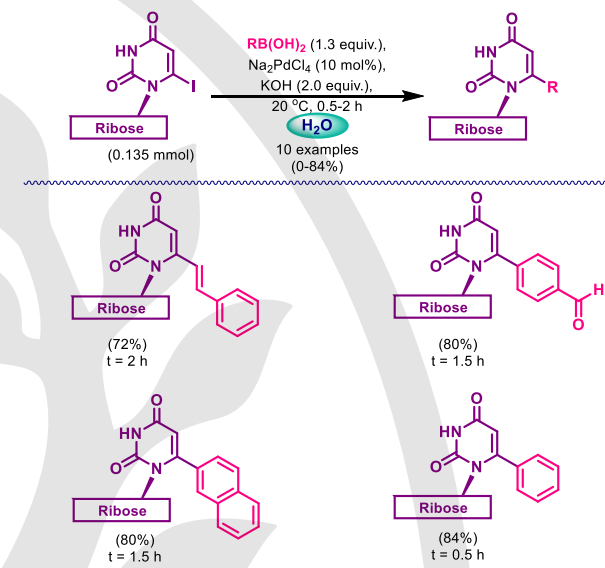


^aNa₂PdCl₄ (0.1 mol%), ^bNa₂PdCl₄ (0.05 mol%).

Scheme 20 Microwave-assisted Suzuki–Miyaura cross-coupling of 5-iodouridine with arylboronic acid in pure water.

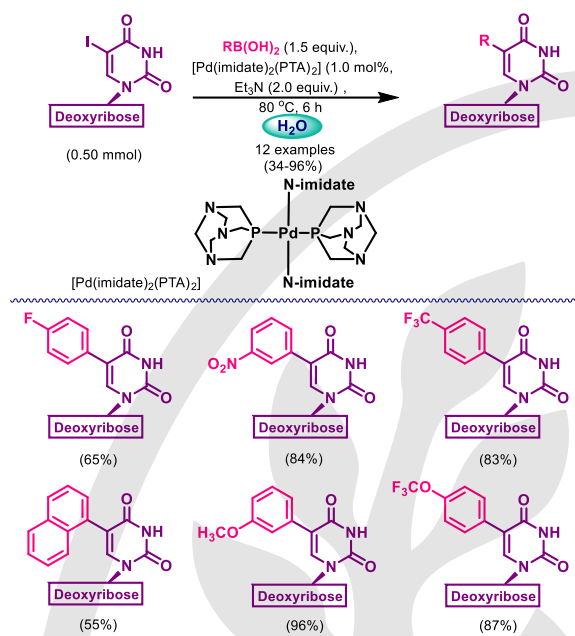
Another methodology involving the Suzuki–Miyaura cross-coupling under microwave conditions in water as the reaction solvent was further reported by Len and co-workers¹⁷⁹ (Scheme 20). This methodology was an enhanced protocol than the previously reported work and demonstrated the improved ligand-free, microwave-assisted Suzuki–Miyaura cross-coupling

of 5-iodo-2'-deoxyuridine using low catalyst loading of Pd catalyst (0.05–0.1 mol%) resulting into a marked improvement in the catalytic efficiency. Reaction time was also shortened, and higher yields of desired products were obtained. The protocol was effective in providing several functionalized 5-iodo-2'-deoxyuridine.



Scheme 21 Synthesis of 6-arylyridines via Suzuki–Miyaura coupling at room temperature in water.

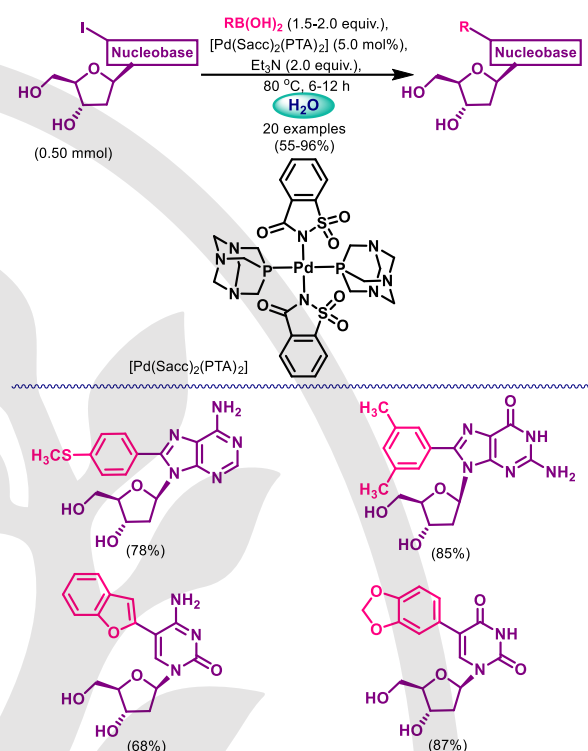
Previous protocols focussed on the functionalization of 5-iodo-2'-deoxyuridine which certainly is of importance to synthetic chemists but the functionalization at other positions of the base substructure also garners a lot of interest among researchers. Keeping this in mind, Len and co-workers¹⁸⁰ in 2013, reported a room temperature protocol for the synthesis of 6-arylyridines via Suzuki–Miyaura cross-coupling reaction in aqueous media under ligand-free condition (Scheme 21). The authors carried out the reaction of 6-iodouridine with different arylboronic acids in the presence of Na₂PdCl₄ as the catalyst and KOH as the base at ambient temperature (25°C).



Scheme 22 Synthesis of C5-arylated pyrimidine nucleosides via Suzuki-Miyaura Coupling reaction.

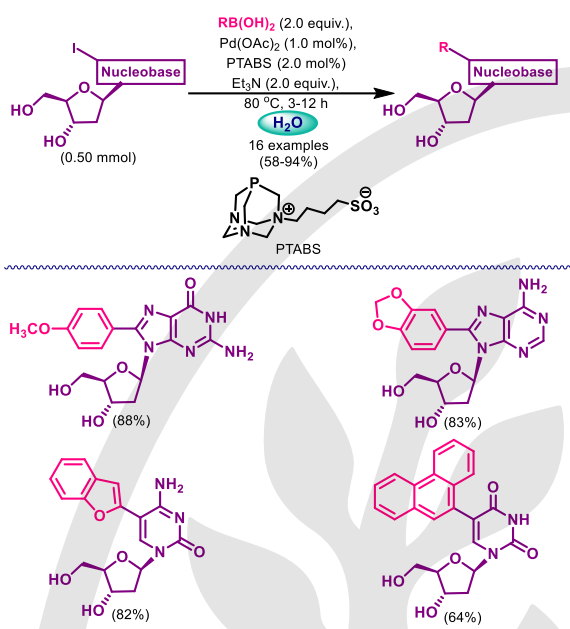
6-Aryluridine analogs were obtained in good yields and a wide variety of functionalities were tolerated containing electron-donating as well as electron-withdrawing groups, especially in the para position of arylboronic acids that were used as the coupling reagents. The procedure was made simple, economical as no protection/deprotection steps were included, and greener with the use of neat water as a solvent.

Despite the advancements taking place in the arena of nucleoside modifications using Suzuki-Miyaura cross-coupling, reaction conditions such as higher reaction temperature, lower catalytic yields and limited substrate scope (other than uridines, not much had been reported on other nucleosides) have plagued these protocols. To address these issues, Kapdi, Serrano, and co-workers¹⁸¹ reported a series of water-soluble Pd-imidate complexes as highly efficient catalysts for the synthesis of C5-arylated pyrimidine 2'-deoxyribose nucleosides as well as C-8 arylated purine 2'-deoxyribose nucleosides (Scheme 22). The synthetic methodology initiated from the arylation of 5-iodo-2'-deoxyuridine with arylboronic acids, $[\text{Pd}(\text{imidate})_2(\text{PTA})_2]$ (1.0 mol%) as the catalyst, triethylamine (NEt_3) as a base (2.0 equiv.) and water as solvent. Developed protocol gives access to a functionalized 5-arylated-2'-deoxyridines in good to excellent yields incorporating functionalities such as electron-rich and electron-withdrawing arylboronic acid. They further reported a good yield of a 5-arylated-2'-deoxyribose nucleoside with naphthalene boronic acids, which are synthetically challenging due to their nucleophilic nature. This was a preliminary report by the authors to show the versatility of the developed catalytic system $[\text{Pd}(\text{imidate})_2(\text{PTA})_2]$ wherein imidate saccharinate was found to be the most effective.



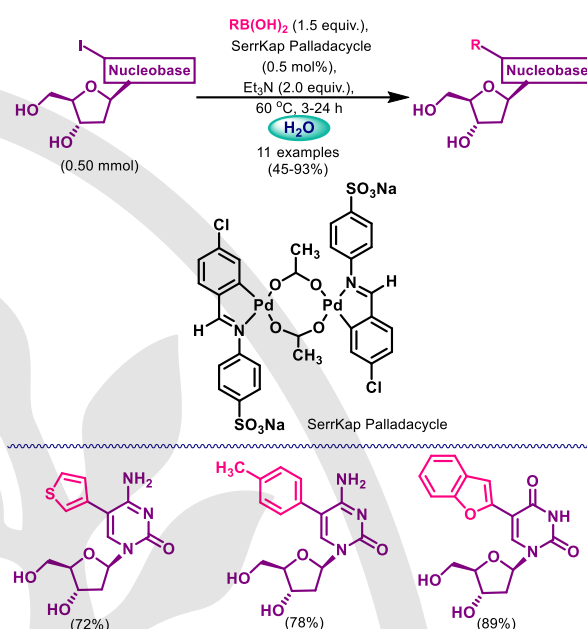
Scheme 23 Synthesis of C5-substituted pyrimidine and C8-substituted purine nucleosides using a water-soluble Pd-imidate complex.

In continuation of the improved reactivity of the $[\text{Pd}(\text{saccharinate})_2(\text{PTA})_2]$ complex towards the Suzuki-Miyaura cross-coupling of 5-iodo-2'-deoxyuridine Kapdi and co-workers¹⁸² further undertook an extensive study for the development of the first catalytic protocol allowing the functionalization of both pyrimidine as well as purine 2'-deoxy nucleosides. An extensive optimization was performed by the research group and the developed $[\text{Pd}(\text{saccharinate})_2(\text{PTA})_2]$ was able to provide direct access to a large variety of functionalized C5-substituted pyrimidine and C8-substituted purine 2'-deoxy nucleosides. Under mild reaction conditions, $[\text{Pd}(\text{saccharinate})_2(\text{PTA})_2]$ was able to activate iodo derivatives of purine and pyrimidine 2'-deoxy nucleosides with aryl as well as heteroarylboronic acids in the presence of NEt_3 (2.0 equiv.) as the base, and water as a solvent at 80°C (Scheme 23). They obtained good to excellent yields for unprotected nucleosides in 6-12 h. This development marked a significant advancement in the arena of nucleoside modification as a single catalyst can perform both pyrimidine and purine modifications effectively rather than using different catalytic systems as reported in literature.



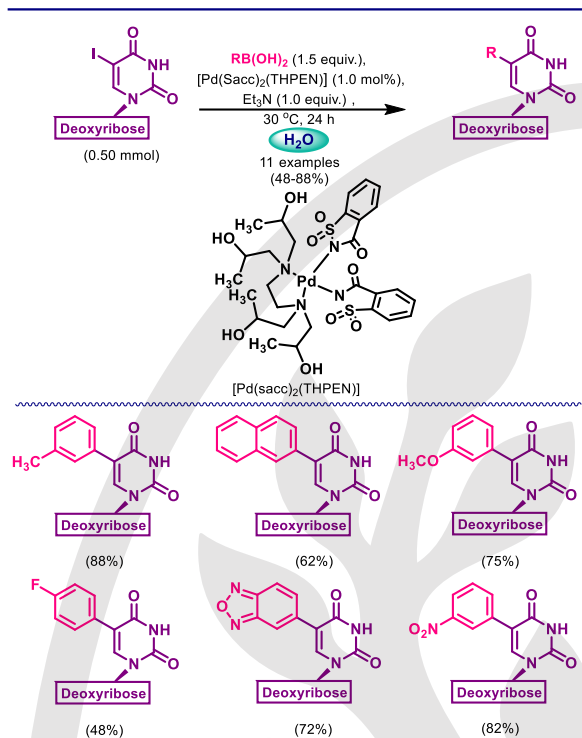
Scheme 24 Suzuki-Miyaura coupling of iodonucleoside with arylboronic acid in water.

The development in the functionalization of purine and pyrimidine nucleosides came at a point when the biological importance of modified nucleosides in the field of antivirals, anticancer drugs, and as fluorescent biological probes was on an exponential trajectory.¹⁸³⁻¹⁸⁶ The requirement of more efficient catalytic systems that can provide easy access to these compounds was certainly of interest to chemists and accordingly, Kapdi and co-workers¹⁸⁷ again came up with an efficient Pd-based catalytic system involving the use of a highly water-soluble phosphine ligand, PTABS (Kapidphos) demonstrating an efficient route for the Suzuki-Miyaura reaction of nucleoside in aqueous media (Scheme 24). Catalytic reactions were performed at lower catalyst loading than the previously reported protocol involving [Pd(saccharinate)₂(PTA)₂] and the isolation of the product was achieved using a column-free method (via simple filtration) as the Pd/PTABS system exhibited high water solubility and stability therefore avoiding leaching of the metal (as confirmed by the ICP-AES of the isolated product). The effectiveness of the catalyst allowed the cross-coupling of all four 2'-deoxy nucleosides in good to excellent yields in water. The catalyst combination also was tested for catalyzing a copper-free Sonogashira coupling of halonucleoside with phenyl acetylene although in the mixed H₂O/CH₃CN solvent system due to the lower solubility of the acetylene substrate yielding 75% of the desired product in 45 min. It is to be noted that the developed protocol proved to be simple, efficient and can be considered a step towards green and sustainable synthesis in nucleoside chemistry.



Scheme 25 Synthesis of modified nucleoside via Suzuki-Miyaura coupling in aqueous media at low temperature.

The desire in developing any catalytic systems for cross-coupling of substrates would be to achieve these transformations under ambient temperature conditions and many such examples have been reported for general substrates. Especially around nucleoside modifications, this could prove to be crucial due to the temperature lability of the nucleoside analogs, but it can also open the possibility of applying the catalytic system for the late-stage modifications of oligonucleotides, DNA or RNA for which catalytic systems are known but less explored and less efficient. Improving upon their previous contributions for the Suzuki-Miyaura transformation of 2'-deoxyribose nucleosides, Serrano, Kapdi, and co-workers¹⁸⁸ developed a phosphine-free palladacyclic complex (SerrKap) for carrying out low-temperature Suzuki-Miyaura modification of nucleosides in aqueous media (Scheme 25). This was the first example of functionalization of 5-iodo-2'-deoxyuridine without any added phosphine/*N*-heterocyclic carbene ligand. The authors carried out the reaction with lower catalyst loading (0.5 mol%) in water as the sole solvent at 60 °C for 24 h and obtained the desired products in good to excellent yields. They further elaborated their study towards the synthesis of modified 2'-deoxycytidine derivatives and like 2'-deoxyuridine obtained good to moderate yields of the desired product. Ambient temperature Suzuki-Miyaura cross-coupling of aryl and heteroaryl halides has been achieved by several research groups using a combination of metal precursors (more commonly Pd) with electron-rich ligands (phosphines or *N*-heterocyclic carbenes) in volatile organic solvents.¹⁸⁹⁻¹⁹¹ These catalytic systems, however, fail to furnish any cross-coupled products when water has been employed as the solvent due to the possible degradation of the catalyst in aqueous media (less compatible).

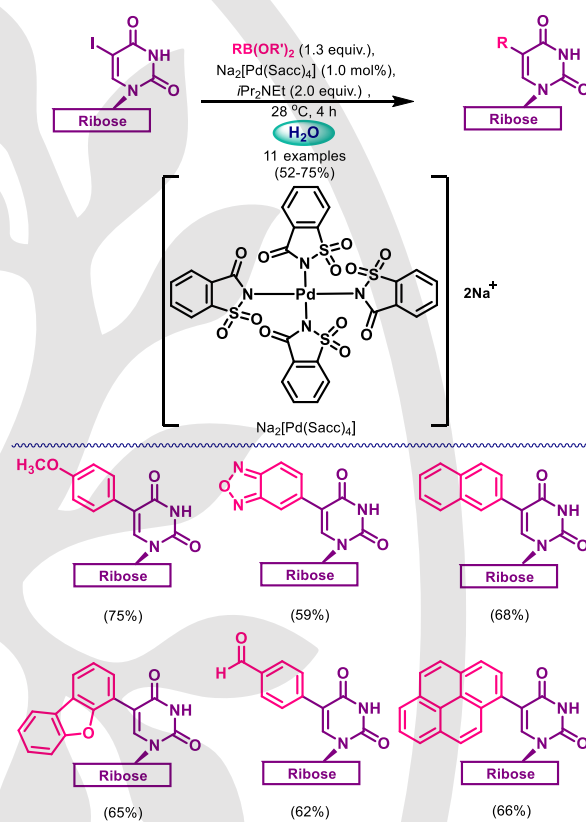


Scheme 26 Synthesis of modified nucleoside via Suzuki-Miyaura coupling in aqueous media at room temperature.

A similar situation has been observed for the modification of nucleosides as electron-rich phosphines have proven to be ineffective and many times either the employment of π -acceptor phosphines such as PTABS (KapdiPhos) in combination with Pd-precursor or ligand-free Pd-catalysts have furnished more promising results albeit at slightly higher temperature. Accordingly, in 2022 Serrano, Kapdi, and co-workers¹⁹² were able to solve this conundrum by the development of another highly active phosphine-free Pd-based precatalysts $[\text{Pd(Sacc)}_2(\text{THPEN})]$ allowing the room-temperature Suzuki-Miyaura cross-coupling of 2'-deoxyribose nucleoside analogues in aqueous media (Scheme 26). Good to excellent yields of the functionalized 2'-deoxyribose nucleosides were obtained which sets the stage of the catalytic system to be further applied to the late-stage modification of oligonucleotides, DNA or RNA in the near future at room temperature.

All the previous examples were pertaining to the modification of the 2'-deoxypurine/pyrimidine nucleosides as the requirement of derivatized analogs in DNA-related research have escalated dramatically in the past decade. However, on the other hand, Suzuki-Miyaura cross-coupling protocols for accessing functionalized ribose nucleoside analogs are limited and mostly performed on protected ribose nucleosides in volatile organic solvents. Development of an effective synthetic protocol to address this gap was undertaken by Serrano, Kapdi and co-workers¹⁹³ and a phosphine-free, water-soluble catalyst $\text{Na}_2[\text{Pd(sacc)}_4]$ provided the desired result when previously developed catalytic system have fallen short for the modification of nucleosides to be performed at room temperature. Serrano, Kapdi and co-workers accordingly have demonstrated a protocol for synthesizing modified ribose nucleosides involving the phosphine-free, water-soluble catalyst

$\text{Na}_2[\text{Pd(sacc)}_4]$ that catalyzes Suzuki-Miyaura coupling reaction of ribose nucleosides (uridine) with different arylboronic acids (Scheme 27). The developed protocol involves $\text{Na}_2[\text{Pd(sacc)}_4]$ (1.0 mol%) as catalyst for the coupling of 5-iodouridine with arylboronic acids in aqueous media at room temperature yielding good to moderate yields of the desired products (Scheme 26). Significant improvement in the reaction time (4 h) was also achieved using the developed catalyst as in most reported protocols reactions were taking 24 h.

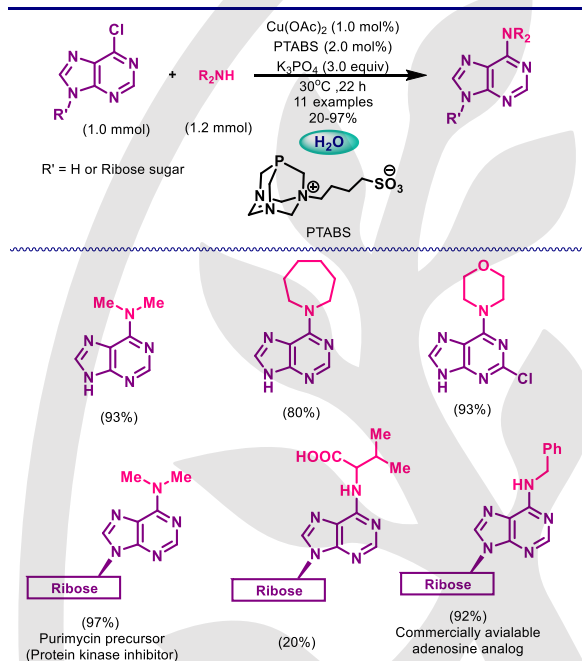


Scheme 27 Synthesis of modified ribose nucleoside via Suzuki-Miyaura coupling in aqueous media at room temperature.

3.1.3. Amination

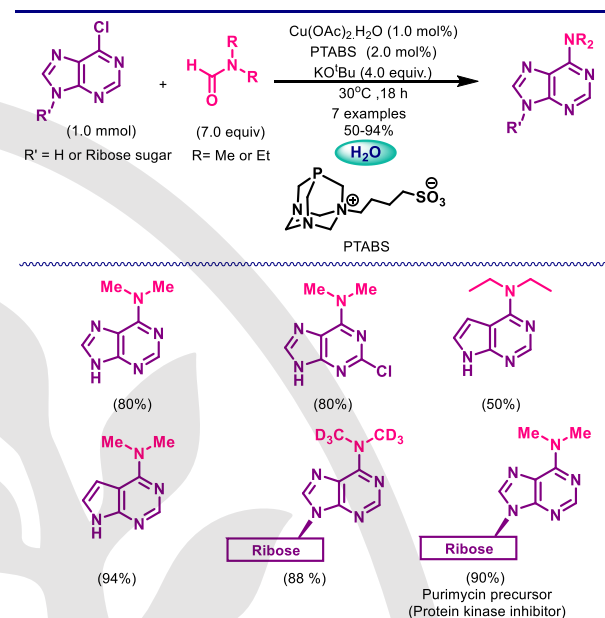
C—N bond formation has gained a lot of importance due to the extensive occurrence of aryl/heteroaryl amines in pharmaceuticals, natural products, organic materials, and catalysts.¹⁹⁴ The exploration of C—N bond formation in nucleosides is of significant interest due to the occurrence of amine-functionalized purine or purine ribosides in various pharmaceutically active molecules, including puromycin, underscores their importance.^{195,196} The controlled introduction of the amino group was first documented by Ullmann¹⁹⁷ and Goldberg¹⁹⁸ using copper metal over a century ago. Significant advancements have been made in the palladium-catalyzed amination of heteroaryl chlorides, with extensive research conducted by Buchwald et al.,¹⁹⁹ Organ et al.,²⁰⁰ and Reetz et al.²⁰¹ at elevated temperatures and using organic solvents.^{202,203} Several research groups, such as Koomen et al.,²⁰⁴ Lanver and Schmalz,²⁰⁵ and Lakshman et al.,^{15,206} Kapdi et al.,²⁰⁷⁻²⁰⁹ have in recent years reported the amination process for nucleosides using palladium

catalysis. However, these methodologies present several limitations, such as the requirement for increased catalyst concentrations, a narrow substrate scope, high reaction temperatures, and the use of organic solvents. Hence, forming a C–N bond under mild and inexpensive reaction conditions remains challenging. Especially the possibility of conducting amination reactions in water remains a distant possibility due to the water-sensitivity of the various catalytic systems used previously.



Scheme 28 Amination of chloropurines and chloronucleosides in water as a solvent.

In 2021, Kapdi and co-workers²¹⁰ successfully addressed these challenges by conducting the amination reaction of chloroheteroarenes, purines, and purine ribose in water for the first time. They employed a water-soluble $\text{Cu}(\text{OAc})_2/\text{PTABS}$ (KapdiPhos) catalytic system along with K_3PO_4 as a base at room temperature, which yielded good to excellent yields of the amination products (Scheme 28). The coupling of 6-chloropurine riboside with various secondary amines produced satisfactory to excellent yields. Notably, the reaction of benzylamine with 6-chloropurine riboside yielded a product with 92% yield, which has been recognized as a highly useful analog of adenosine in commercial applications. Furthermore, the authors demonstrated the functionalization of 6-chloropurine riboside with valine amino acid in water for the first time.

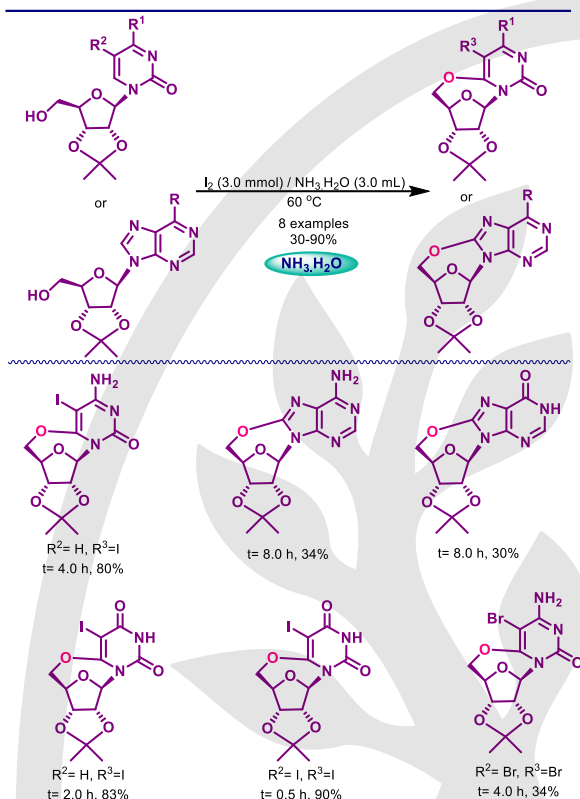


Scheme 29 *N,N*-dialkylamination of chloropurines and chloronucleosides.

The increased solubility of purines in water led to a more intricate column-free isolation process than the typical heteroarenes which were also aminated using the same protocol. Remarkably, the catalyst also provided an opportunity to recycle the catalytic solution for up to 12 cycles in water. Scale-up reactions were also performed furnishing excellent yield of the coupled product while the recovery of the utilized water (as a solvent) was also carried out to make it a truly sustainable synthetic methodology.

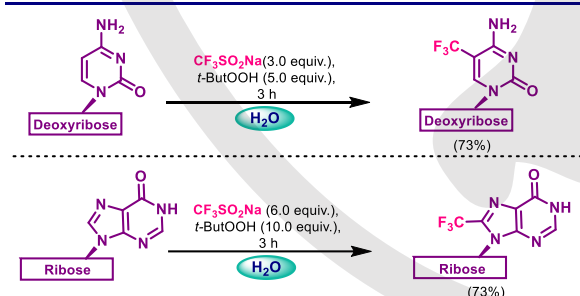
Amination of aromatic and heteroaromatic substrates with gaseous amines is a major synthetic challenge in academia as well as industry due to the complications related to the storage, transportation and hazards associated with the gases.^{211,212} Dialkylamine is one such gaseous amine that is a key component in various synthesis processes and is commonly found in agrochemicals and pharmaceuticals. Limited studies have focused on the dimethylamination of chloroheteroarenes through in situ DMF decomposition. Despite the few examples in literature, expensive palladium catalysts have been predominantly used. Hence, in 2022, Kapdi and co-workers²⁰⁸ reported the *N,N*-dimethylamination of chloroheteroarenes, chloropurines, and chloropurine ribose using Cu/PTABS system via in-situ generation of *N,N*-dimethylamine using DMF as a surrogate molecule and water as an additive at room temperature. 6-Chloropurine, 6-chloro-7-deazapurine, 2,6-dichloropurine, and 2-amino-6-chloropurine were subjected to the developed protocol, which provided good to excellent *N,N*-dialkylamination products. The established method has proven successful in synthesizing deuterated dialkylaminated purines and purine ribose using deuterated dimethylformamide and important drugs like puromycin precursor. Even though DMF was used as the source of dimethylamine gas, the authors have explicitly indicated that the reaction can also be exclusively performed in water as the sole solvent as the catalytic system is very much compatible.

3.1.4. Miscellaneous Reactions in Water



Scheme 30 Synthesis of C-5-Substituted $O^6,5'$ -Cyclopyrimidine Nucleoside Analogues in Ammonia Water.

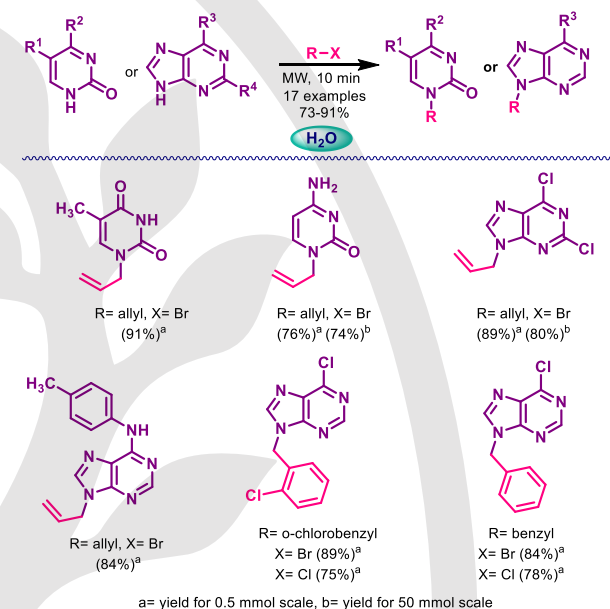
Cyclonucleosides are useful synthetic intermediates, with potential biological impact on enzymatic repair processes. They are also crucial in nucleoside configurational studies.^{213–215} In 2013, Guo and co-workers²¹⁶ demonstrated an efficient, one-step process for synthesizing C-5-substituted $O^6,5'$ -cyclopyrimidine nucleoside analogs using molecular iodine in ammonia-water at 60°C, resulting in good yields (Scheme 30). Ammonia-water acts as both a base and a solvent, eliminating the need for organic solvents. This approach yielded satisfactory results for purine cyclonucleosides but wasn't suitable for unprotected pyrimidine nucleosides, resulting in low yields of the corresponding pyrimidine cyclonucleosides.



Scheme 31. Trifluoromethylation of nucleosides using CF_3SO_2Na /*tert*-butyl-hydroperoxide (*t*BuOOH) system in aqueous media.

Introduction of a trifluoromethyl group into low molecular weight compounds often enhances their bioactivity by

increasing the lipophilicity of the associated molecular scaffolds, thereby facilitating improved cellular uptake.^{217–220} In 2013, Montesarchio and co-workers²²¹ developed a mild protocol for the synthesis of 5- CF_3 -2'-deoxycytidine, 8- CF_3 -2'-deoxyadenosine, 8- CF_3 -2'-deoxyguanosine and 8- CF_3 -inosine derivatives utilizing a CF_3SO_2Na /*tert*-butyl-hydroperoxide (*t*BuOOH) system in aqueous conditions at ambient temperature, achieving good yields (Scheme 31).



Scheme 32 alkylation at $N1$ and $N9$ position of purines and pyrimidines under microwave conditions using water as solvent.

However, the yields for 2'-deoxyguanosine and 2'-deoxyadenosine were lower than that of 2'-deoxycytidine which is attributed to their limited solubility in water and the glycosidic bond cleavage under the conditions. Consequently, a biphasic solvent system was employed for the trifluorination of 2'-deoxyguanosine and 2'-deoxyadenosine, necessitating a three-step process. Preliminary in-vitro bio screenings revealed an intriguing dose-dependent antiproliferative activity of the synthesized derivatives. Notably, 5-trifluoromethyl-2'-deoxycytidine exhibited significant antitumor activity, while the 8-trifluoromethylated derivatives of 2'-deoxyadenosine and 2'-deoxyguanosine also demonstrated potential as antitumor agents.

Unsaturated bonds are significant in the carbohydrate cycles associated with various drugs and bioactive compounds. The introduction of unsaturation or an alkene functionality on to the sugar moiety of nucleosides can certainly help improve the bioactivity as these acyclic nucleosides have been studied extensively in literature.^{222–225} In 2016, Xia and Sun²²⁶ performed a regioselective alkylation at $N1$ and $N9$ positions of purines and pyrimidines under microwave condition using water as a solvent, resulting into a series of acyclic nucleoside analogs containing unsaturated functionality on the sugar moiety in good to excellent yields (Scheme 32). A wide variety of functionalities such as allyl, benzyl, and substituted benzyl were well tolerated. However, reduced yields were observed when electron-withdrawing groups were present at C5 position of pyrimidine, as compared to the presence of electron-donating groups. Furthermore, this technique eliminated the requirement for protecting hydroxyl and amino

groups which was necessary in the previous reported protocols. The reaction was successfully scaled up to a 50 mmol scale, and product purification was achieved through recrystallization instead of the more laborious chromatography method, making it suitable for industrial applications

This section discussed at length several known examples of functionalization of ribose and 2'-deoxyribose nucleoside modifications conducted in water as the sole reaction solvent. Although water provides a sustainable alternative to the usage of environmentally polluting volatile organic solvents, there certainly are questions about its usage too given the problems associated with the limited availability of drinkable water sources, and further contamination could pose a major environmental problem. Therefore, it is very important to recover the water used during the reaction as well as possibly conduct several recycles of the catalytic solutions to achieve sustainability.

4. Deep Eutectic Solvents

Previous sections discussed in detail the usefulness and importance of ionic liquids and water as sustainable solvents with each having several issues that limit their applications beyond academia. Deep eutectic solvents (DES) have been in recent years identified as a suitable alternative to the ionic liquids due to the special properties offered by them. DES are environmentally benign solvents formed from the combination of two or more substances and have melting points lower than that of the individual components due to hydrogen bonding interactions.^{227,228} The term "eutectic" was first introduced by British physicist F. Guthrie in 1884,²²⁹ while the concept of DES was introduced by Abbott et al. in 2003. Abbott first synthesized DES by mixing choline chloride and urea, resulting in a liquid with an eutectic melting point of 12°C.²³⁰ DES are useful in sustainable chemistry for their biodegradability and low toxicity, making them suitable for various applications, including electrochemistry, organic synthesis, biotransformation, and catalysis.^{231–233}

DES are often compared with ionic liquids (ILs) due to their similarities, such as high thermal stability, low volatility, and low vapor pressure. However, DES offers advantages over traditional ILs, including more straightforward synthesis, lower cost, and less environmental impact as many times they are a combination of biocompatible substrates. They effectively address issues like moisture sensitivity and high costs associated with some ILs.^{152,234} However, nucleoside chemistry in ILs is more common than in DES. In biocatalysis, DES has proven beneficial compared to aqueous solvents and polar organic solvents such as acetone, DMSO, or methanol which can denature enzymes. DES allows for the dissolution of substrates while maintaining enzyme activity. Research has shown that DES can support various biocatalytic processes, such as lipase-catalyzed transesterification, aminolysis, epoxide hydrolysis, *N*-alkylation of aromatic amines, and Knoevenagel condensation, often achieving comparable or superior rates and selectivity relative to conventional organic solvents.^{235–238}

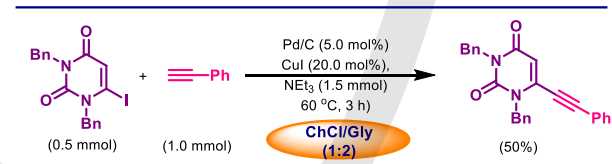
Despite their many advantages, DES have been relatively underexplored in nucleoside chemistry. This is primarily due to

the high polarity of nucleosides and the fact that DES does not offer the same level of solubility for nucleosides as ILs or water. The following section will address the modification of nucleosides using DES.

4.1. Modification of Nucleobase Moiety

4.1.1 Sonogashira Coupling

Significant modifications in pyrimidine and purine moieties, through the introduction of aryl, polyaryl, heteroaryl, heteropolyaryl, alkenyl, and alkynyl groups via C—C cross-coupling, have been explored to study biological environments like DNA and RNA structural probes, protein-DNA complexes, DNA damage, mutation, and cancers. The palladium-catalyzed Sonogashira coupling reaction is effective for alkyne group installation and has emerged as a crucial synthetic tool in recent years. This method facilitated the synthesis of fluorescent nucleosides for biological probe applications.^{239–241} In 1975, Sonogashira, Hagihara, and Tohda reported the Pd(PPh₃)₂Cl₂ catalyzed reaction involving CuI as the co-catalyst and amine as the base.²⁴² Subsequent modifications have employed various catalysts, additives, and ligands under diverse conditions. However, using copper salts can negatively impact catalysis and require stoichiometric amounts of copper co-catalyst, which may contaminate the modified nucleosides.¹⁸⁷ Consequently, significant research focuses on developing copper-free and preferably amine-free Sonogashira catalytic systems. In recent decades, nearly 40% of the Sonogashira coupling reactions have been conducted in *N,N*-dimethylformamide (DMF), a toxic solvent.²⁴³ Hence, recent advances in Sonogashira reaction protocols have emphasized on developing eco-friendly methodologies, including reactions conducted in water or aqueous organic solvent mixtures, glycerol, and under aqueous micellar conditions with surfactants as additives. In nucleoside chemistry, only a few methodologies have been employed for the alkylation of purines and pyrimidines, and these typically involve water-organic solvent mixtures.^{158,244}



Scheme 33 Sonogashira coupling of 6-iodouracil derivative under using ChCl/Gly deep eutectic solvent.

Uracil derivatives are valuable frameworks in drug discovery, showing various biological and pharmacological properties.^{245,246} Few studies have explored using DESs or low melting mixtures (LMMs) for Sonogashira coupling. Notable contributions include Fuxiang et al. (2009),²⁴⁷ König and Ilgen (2009),²⁴⁸ and Ramón, Alonso, and Guillena et al. (2017 and 2019),^{249,250} who conducted Sonogashira couplings using various eutectic mixtures. A commonality among these procedures is the necessity of a suitable ligand complexed with palladium. Ligand-free Sonogashira coupling reactions in eco-friendly unconventional solvents are relatively rare.

In 2020, Capriati, Salomone, and colleagues²⁵¹ illustrated the

ligand-free Pd/C catalyzed Sonogashira cross-coupling of (hetero)aryl iodides and protected 6-iodouracil derivative utilizing a choline chloride/glycerol eutectic mixture as an environmentally friendly solvent (Scheme 33). The authors primarily demonstrated the coupling of various (hetero)aryl iodides with aromatic and aliphatic alkynes without the need for copper as a co-catalyst. They also explored the effectiveness of the developed methodology for a 6-iodouracil derivative. The 6-iodouracil derivative was cross-coupled with phenylacetylene in the presence of CuI (20 mol%) at 60 °C, resulting in a 50% yield of the desired product. One advantage of this approach is its ability to successfully apply to electron-rich iodides, which are typically challenging substrates for Sonogashira coupling. Furthermore, the eutectic mixture and the catalyst can be reused for up to four cycles. While significant progress in nucleoside chemistry using DES has not been achieved, this solvent could be a promising choice for future advancements.

5. 2-Methyl tetrahydrofuran

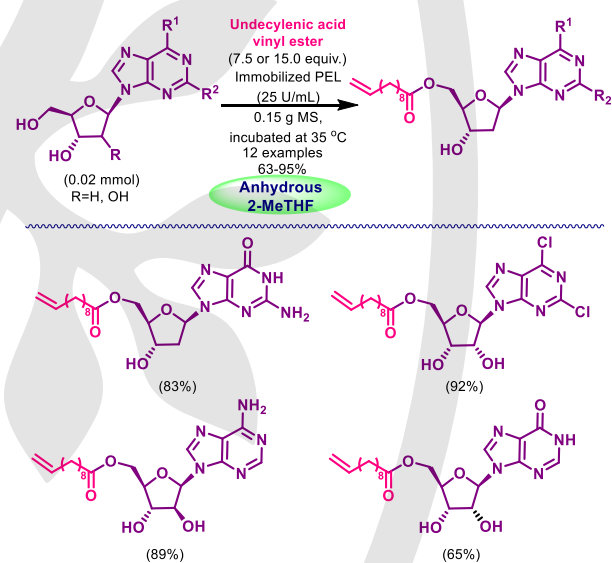
2-Methyltetrahydrofuran (2-MeTHF) is a readily available, cost-effective, and environmentally friendly solvent derived from renewable biomass, specifically from furfural obtained from corn, sugar cane bagasse, and oat hulls.^{26,252} Substituting 2-MeTHF for traditional solvents such as tetrahydrofuran (THF), dichloromethane, or dichloroethane promotes greener chemical processes by adhering to reduction, recycling, and reuse principles. 2-MeTHF, a cyclic ether with a higher boiling point (80 °C) than THF (66 °C), minimizes solvent evaporation during reactions. It also demonstrates superior resistance to hydrochloric acid compared to THF while the lower possibilities of forming the dangerous peroxides also make 2-MeTHF more suitable for usage.²⁵³ Preliminary toxicological studies have not linked 2-MeTHF to genotoxicity or mutagenicity, enhancing its safety profile.²⁵⁴ As a result, 2-MeTHF is increasingly employed as a replacement for THF in various applications, including the preparation of Grignard reagents,²⁵⁵ low-temperature lithiation,²⁵⁶ lithium aluminum hydride reductions, the Reformatsky reaction,²⁵⁷ and metal-catalyzed coupling reactions^{258,259} but less explored in the nucleoside chemistry field. Additionally, 2-MeTHF has shown promise in lipase-catalyzed transesterification^{260,261} and other chemical processes, demonstrating its utility and effectiveness as a bio-based solvent.

Nucleosides, characterized by their polar nature due to multiple hydroxyl and amino groups, are poorly soluble in non-polar solvents. Consequently, polar solvents such as tetrahydrofuran (THF), pyridine, and binary solvent mixtures have been traditionally employed for the enzymatic acylation of nucleosides, as they offer satisfactory solubility.^{262,263} However, the polar solvents can deactivate enzymes, limiting enzymatic processes' effectiveness.^{264,265} 2-MeTHF is more compatible with enzymes compared to THF. Hence, nowadays, researchers have started using 2-methyltetrahydrofuran (2-MeTHF) as an alternative to other polar solvents for the enzymatic acylation of the 5'-hydroxyl group of nucleosides. This topic will be discussed in detail in the next section.

5.1. Modification of Sugar Moiety

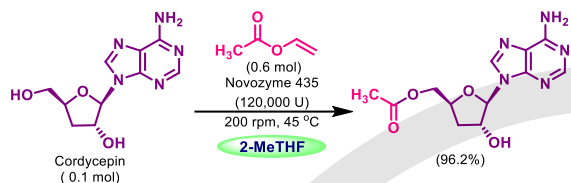
5.1.1 Acylation of 5'-OH

Nucleosides are crucial polyhydroxylated compounds with significant applications as antiviral and antitumor agents.^{266,267} Despite their therapeutic benefits, these nucleoside drugs often exhibit low oral bioavailability and short plasma half-lives due to their high polarity and rapid cleavage of the glycosyl bond by nucleoside phosphorylase.^{266,268} To address these limitations, acylation of nucleosides has proven beneficial. For example, valganciclovir,²⁶⁹ an ester derivative of ganciclovir,²⁷⁰ shows improved therapeutic efficacy compared to its parent drug. However, regioselective chemical acylation of nucleosides remains a complex and labor-intensive process involving multiple protection and deprotection steps. Enzymatic methods offer a promising alternative, providing regiospecific 5'-OH acylation with mild reaction conditions and reduced environmental impact, thus presenting a more efficient and eco-friendly approach for nucleoside modification.^{271,272}



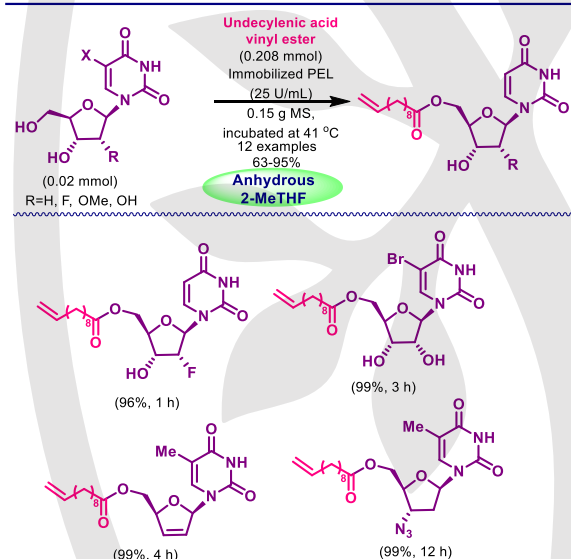
Scheme 34 Enzyme-catalyzed acylation of cordycepin in anhydrous 2-MeTHF solvent.

In 2012, Li, Zong, and co-workers²⁷³ demonstrated a regioselective enzyme acylation of 8-chloroadenosine and its analogs in MeTHF using immobilized *Penicillium expansum* lipase (PEL). The 5'-O-regioselectivity depended on the nucleoside structures, particularly the 2'-substituents. The lipase-catalyzed regioselective undecylenoylation of purine nucleosides was carried out with 25 U/mL of immobilized enzyme, 7.5 to 15.0 equiv. of undecylenic acid vinyl ester, and incubated at 35 °C, resulting in yields of acylated products ranging from 63 to 95% and excellent regioselectivities (94→99%). The study revealed that the lipase exhibited enhanced catalytic activity and improved thermostability in MeTHF compared to other organic solvents and co-solvent systems. The use of solvents derived from biomass holds the potential to open up new avenues for environmentally friendly and sustainable biocatalytic processes.



Scheme 35 Enzyme-catalyzed regioselective undecylenoylation of 8-chloroadenosine and its derivative.

Cordycepin possess a wide range of interesting biological and pharmacological activities, but it undergoes rapid hydrolytic deamination by adenosine deaminase (ADA). Cordycepin exhibits hydrophilic properties, making it challenging to pass through cell membranes via passive diffusion. Several studies have suggested that fatty acid ester derivatives have the potential to serve as effective prodrugs for numerous nucleoside drugs. Thus, the acylation of cordycepin will help prevent rapid deamination and increase its pharmacological activity. In 2013, Chen and co-workers²⁶¹ conducted the first enzyme-catalyzed regioselective acylation of cordycepin using Novozyme 435 and vinyl acetate at 45 °C in an environmentally friendly solvent 2-MeTHF.



Scheme 36 Enzyme-catalyzed acylation of pyrimidine nucleosides in anhydrous 2-MeTHF solvent.

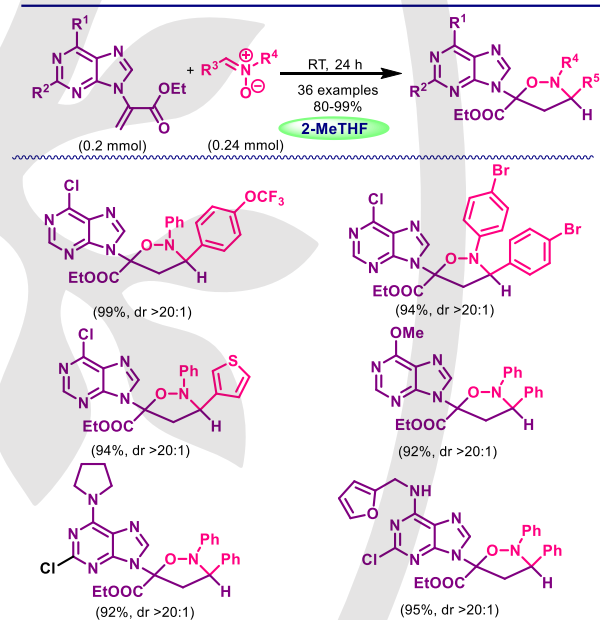
They tested nine lipases and three proteases to assess their effectiveness in enzymatically acylating cordycepin with vinyl acetate in organic media. Novozyme 435 exhibited exceptional operational stability in MeTHF, leading to the most favorable results, characterized by the highest conversion rate and superior initial reaction speed (Scheme 36). The biocatalytic process was found to be applicable for scales of up to 25 grams, yielding 95.2%. Novozym 435 can be recycled for up to 7 cycles to synthesize cordycepin derivative on a 25-g scale.

Later in 2013, the same research group²⁷⁴ employed the PEL enzyme for the regioselective acylation of pyrimidine nucleosides using 2-MeTHF as a solvent and analyzed the interaction between the enzyme and substrate based on the nucleoside structures. They examined the solubility of 5-fluorouridine in four solvents: 2-MeTHF, acetone, acetonitrile,

and THF. Although the nucleoside's solubility was highest in THF, the hydrophobic nature of 2-MeTHF resulted in a lower activation energy (E_a) than the other solvents. As a result, MeTHF demonstrated the highest catalytic activity for the lipase, exceeding that in THF by more than six times.

Additionally, they investigated the impact of 5-substituents found in the base moiety of nucleoside structures on the regioselective enzymatic acylation reaction. Furthermore, the influence of 2'- and 3'-substituents in the sugar moiety was also studied. Halogenated uridine derivatives displayed increased solubility and achieved a conversion rate of 99%. Later, Substituting the 2'-hydroxy group with a hydrophobic methoxy group or fluorine notably enhanced solubility and initial reaction rates. However, minimal impact was seen on the 5'-O-regioselectivity. The absence of a 3'-hydroxyl in the sugar component significantly enhanced nucleoside solubility, although enzymatic acylation rates decreased. The effect of the solvent and structural characteristics of the nucleoside is evident in the results that were obtained.

5.1.2. Miscellaneous Reactions in 2-MeTHF



Scheme 37 Regioselective and diastereoselective [3+2] annulation of α -purine-substituted acrylates with nitrones using 2-MeTHF as a green solvent.

Recently, in 2023 Wang and co-workers²⁷⁵ demonstrated a catalyst-free, regioselective, and diastereoselective [3+2] annulation of α -purine-substituted acrylates with nitrones using 2-MeTHF as an eco-friendly solvent at room temperature for 24 h, resulted in good to excellent yields of the single diastereomeric isoxazolidinyl product (Scheme 37). Various solvents were evaluated, with 2-MeTHF demonstrating the excellent yield and diastereoselectivity of $>20:1$. Steric hindrance, electronic properties, and substituents on the aryl and styryl groups do not affect regio-, diastereoselectivity of the product. The introduction of different substituents at the C2 and C6 positions of the purine skeleton showed minimal impact on the reaction outcome.

6. Solvent-free Reactions

Mechanochemistry is an emerging discipline within organic chemistry that employs mechanical force to form or break the bonds. This approach not only diminishes the reliance on solvents but also accelerates reaction rates and facilitates the synthesis of various products. Additionally, it is attracting interest in the nucleotides, nucleotide and phosphoramidites chemistry, as it lessens exposure to aqueous conditions, thereby reducing or potentially eliminating side reactions associated with solvents and heating.^{276–278} Prior research has thoroughly investigated solid-state reactions with grinding mode.^{279,280} Reactions such as Reformatsky and Luche,²⁸¹ cyclopropanation,²⁸² Aldol condensations,²⁸³ Dieckmann condensations,²⁸⁴ Knoevenagel condensations,²⁸⁵ Reductions,²⁸⁶ Michael addition,²⁸⁷ and phenol coupling reactions²⁸⁸ have been reported. Simplicity, selectivity, and yield are some of the advantages of these reactions. High-speed ball milling has been implemented under solvent-free conditions for reactions such as the synthesis of flavones from β -dicarbonyl compounds,²⁸⁹ dimerization of C_{60} ,²⁹⁰ Horner–Wadsworth–Emmons reaction,²⁹¹ synthesis of polysubstituted pyrroles,²⁹² halogenation of aromatic compounds,²⁹³ etc. This procedure offers rapid conversion of a desired product under solvent-free conditions and requires low catalyst loading. Although this methodology is widely used in the organic chemistry field,²⁹⁴ its application to nucleoside or nucleotide substrates on preparative scales has been limited. But this approach could be viewed as a viable sustainable alternative to conventional solvent practices.

7. Conclusions and Outlooks

Nucleosides and oligonucleotide-based pharmaceutical drugs requirement in the world market has risen exponentially in the past decade. This rise has coincided with the rapid development of synthetic protocols allowing the efficient functionalization of the basic nucleoside unit and has certainly helped industry to cater to these increased demands in a timely manner. However, the ramifications of utilizing large amounts of reagents, solvents for the reactions as well as for the purification has put researchers in academia/industry under increased pressure to develop sustainable synthetic solutions. Volatile organic solvents that are used extensively in these processes have commonly been associated with problems pertaining to environmental pollution, toxicity and risk of explosion. Industry is under increased pressure to identify greener alternatives to the existing technologies mainly in terms of curtailing the usage of VOCs and replacing them effectively with green or sustainable solvents while reducing overall process mass intensity (PMI).²⁹⁵ Academic researchers have led the way to address this crucial issue and have identified several green/sustainable solvents that could provide the desired solution to VOCs. This review details the state-of-the-art in the quest to provide improved sustainability to the modification/functionalization of nucleosides which are the important building blocks for the oligonucleotides/oligonucleotide-based drug synthesis. Solvents such as ionic liquids, water, deep eutectic solvents and

2-MeTHF have been identified and applied effectively to obtain improved yields of the modified nucleosides in various processes. However, this is just the tip of the iceberg and much more needs to be done to address the burning issue in front of the industry of making the oligonucleotide manufacturing process more sustainable by achieving a lower PMI. There should also be an attempt from industry to incorporate some of these methodologies if they offer better yield, improved reaction conditions and therefore help achieve sustainability in manufacturing. Alternatively, the usage of solvents for these processes could also be curtailed by the employment of solvent-less, solvent-free or chromatography-free synthetic protocols utilizing efficient mechanochemical methods such as ball milling that has in recent years demonstrated its effectiveness.²⁹⁶

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Conflict of Interest

The authors declare no conflict of interest.

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