Graphical Abstract

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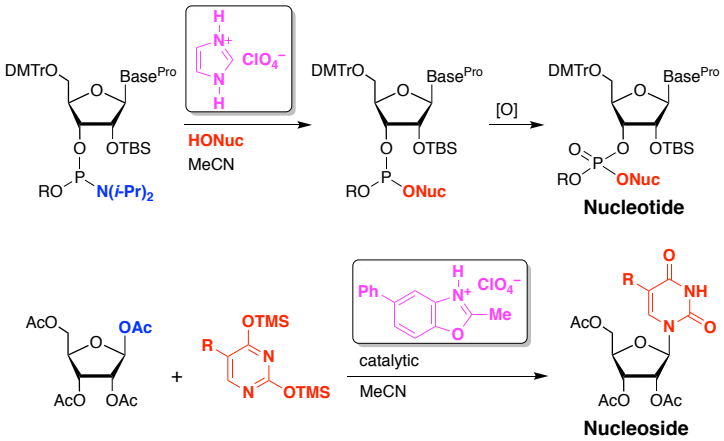
Masaki Tsukamoto and Kin-ichi Oyama



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Recent application of acidic 1,3-azolium salts as promoters in the solution-phase synthesis of nucleosides and nucleotides

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ABSTRACT

Acidic 1,3-azolium salts are prepared from Brønsted acids and 1,3-azoles such as imidazole, thiazole, and oxazole. Acidic imidazolium salts are frequently employed as promoters for the synthesis of nucleotides using the phosphoramidite method in a solution phase. Recently, it was revealed that thiazolium and oxazolium salts catalyzed Vorbrüggen-type *N*-glycosylation reactions to give nucleosides. These reactivities are attributed to the stronger Brønsted acidities of the thiazolium and oxazolium salts relative to those of the imidazolium salts. This digest focuses on recent progress in the applicability of acidic 1,3-azolium salts as promoters in the solution-phase synthesis of nucleosides and nucleotides.

Contents

Introduction

Acidic 1,3-azolium salts are prepared from Brønsted acids and 1,3-azoles such as imidazole, thiazole, and oxazole (Figure 1). These salts have been known for a long time and their physical characteristics have been well investigated by ^{1}H and ^{13}C NMR spectroscopies,[1,2] potentiometric titration,[3] and infrared spectroscopies.[4,5] The pK_a's of protonated imidazole, thiazole, and oxazole derivatives were determined by potentiometric titration, disclosing that the pK_a decreases in this order.[3] It is well known that the non-substituted acidic azolium salts have pK_a values of 7.0, 2.4, and 0.8, respectively (Figure 1).[6]

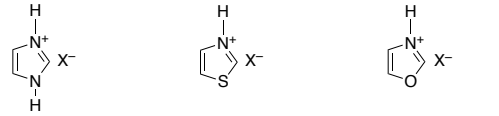

Figure 1. pK_a values of representative acidic 1,3-azolium salts in water. X^- indicates a counter anion.

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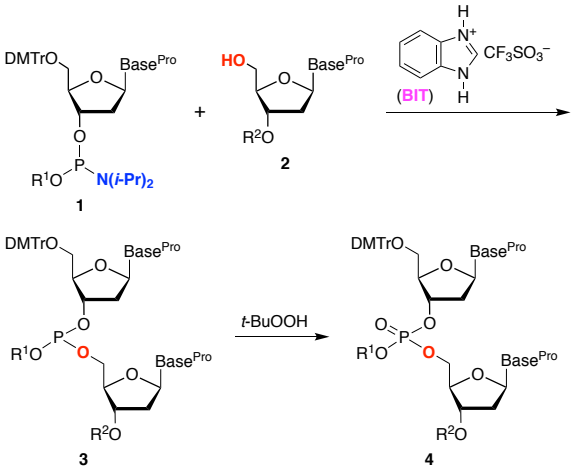
In the first application of a protonated imidazole derivative as a coupling reagent, benzimidazolium triflate (BIT) was used to promote condensation of a nucleoside phosphoramidite and a nucleoside,[7–9] which is a key step for the synthesis of nucleotides and oligonucleotides.[10,11] As shown in Scheme 1, phosphoramidite **1** and nucleoside **2** were condensed with a stoichiometric amount of BIT to form the intermediary phosphite triester **3**, which was subsequently oxidized by *tert*-butyl hydroperoxide[12] to afford the dinucleoside phosphate **4** quantitatively. BIT is compatible with an acid-labile 4,4′-dimethoxytrityl (DMTr) protecting group and is more advantageous than a previously reported acidic pyridinium salt that partially cleaves the DMTr group.[13] Since this report, various combinations of imidazole derivatives and acids have been tested to identify more reactive promoters; several such promoters have already been found.[14,15] At present, acidic imidazolium salts such as BIT and imidazolium perchlorate (IMP) (Figure 2)[16] are employed as promoters for the internucleotide bond formation. The mechanism of this reaction has been well described in comparison with those promoted by 1*H*-tetrazole and its analogs.[14]



Scheme 1. Internucleotide bond formation reaction using benzimidazolium triflate (BIT) as a promoter. Base^{Pro} indicates a protected nucleobase.

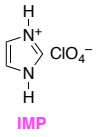


Figure 2. Imidazolium perchlorate (IMP).

The stronger acidity of acidic thiazolium and oxazolium salts compared to imidazolium salts enables the former to promote other types of reactions: thiazolium salts catalyze esterifications[17] and oxazolium salts catalyze Vorbrüggen-type *N*-glycosylation reactions.[18,19] The application of these salts as reagents has just begun.

This digest focuses on the recent examples of solution-phase synthesis of nucleosides and nucleotides up to trinucleotides employing condensation reactions promoted by acidic imidazolium, thiazolium, and oxazolium salts. For applications of acidic imidazolium salts to the synthesis of oligonucleotides, please see the relevant reviews.[20,21] Nucleobases with and without protecting groups that appear in this digest are summarized in Figure 3.

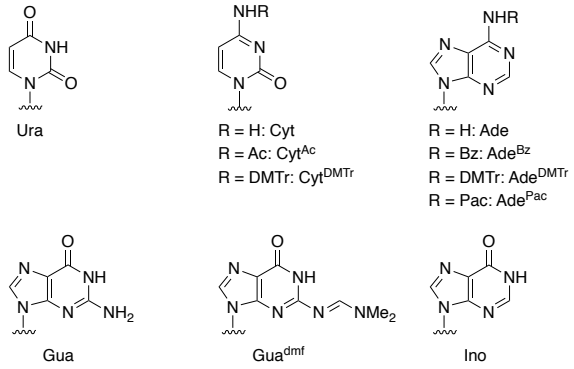


Figure 3. Nucleobases with or without protecting groups. Pac = phenoxyacetyl.

The general structure of an acidic 1,3-azolium salt is shown in Figure 4. A heteroatom or heteroatom group Y (NH, N-alkyl, S, and O) strongly influences the Brønsted acidity,[3,6] while a counter anion X^- functions not only as a nucleophile[18,22] but also as a key factor for the hygroscopicity.[14,18] Substituents R^1, R^2, and R^3 enable control of the hygroscopicity and Brønsted acidity. Reagents with less hygroscopicity are obviously more favorable. In the following examples, the non-hygroscopic salts discovered by screening were employed as promoters or catalysts.[14,18]

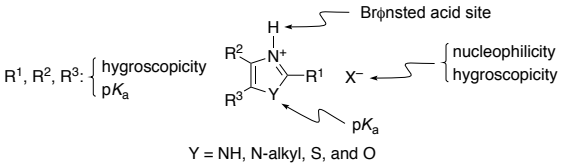


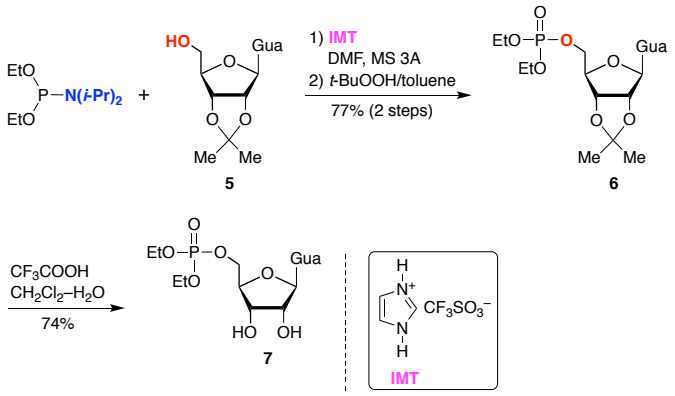
Figure 4. General structure of an acidic 1,3-azolium salt.

Acidic imidazolium salts

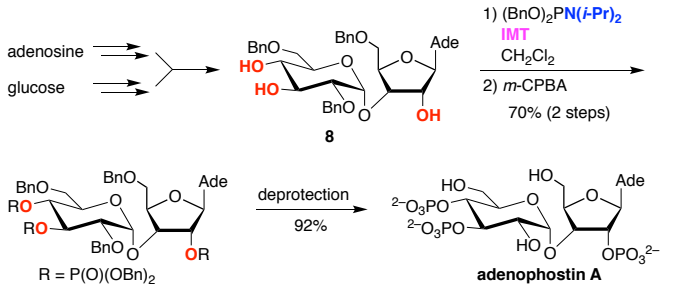
Synthesis of mononucleotides

Diethyl guanosine 5′-monophosphate (**7**) was synthesized by using imidazolium triflate (IMT) for the conformational analysis in the gas phase (Scheme 2).[23] 2′,3′-*O*-Isopropylideneguanosine (**5**) was converted to 5′-*O*-monophosphate **6** by treatment with diethyl diisopropylaminophosphoramidite and IMT followed by oxidation with *tert*-butyl hydroperoxide.[12] Removal of the isopropylidene protector of **6** afforded the target phosphotriester **7**, which was vaporized by pulsed laser desorption and was analyzed by UV and IR spectroscopy. The result suggested the existence of an internal hydrogen-bonding structure between the oxygen atom of the P=O and one of the hydrogen atoms of the amino group in the guanine base.

IMT was uniquely employed for phosphitylations of three secondary hydroxy groups of the adenine-unprotected intermediate **8** derived from adenosine and glucose (Scheme 3).[24] Subsequent oxidation with *m*-CPBA followed by hydrogenolysis of the benzyl groups afforded adenophostin A, a potent D-*myo*-inositol 1,4,5-triphosphate receptor-agonist discovered from a culture broth of *Penicillium brevicompactum*.[25,26] An advantage of IMT is that base-unprotected adenine derivatives can be used as substrates. This tri-phosphitylation procedure has been applied to the synthesis of various adenophostin A analogs.[26–28] As a phosphitylation reagent, *o*-xylene *N*,*N*-diethylphosphoramidite[29] has also been employed.[26,27]

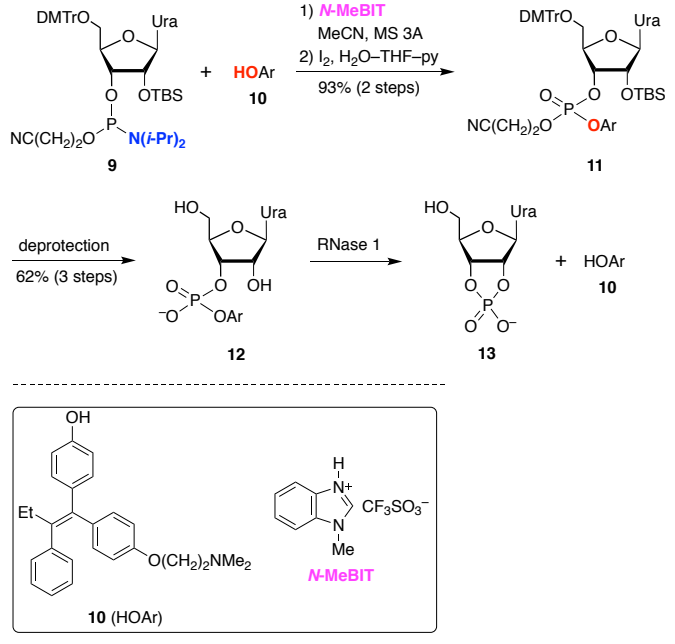


Scheme 2. Synthesis of diethyl guanosine 5′-monophosphate (**7**).



Scheme 3. Final stages in the synthesis of adenophostin A.

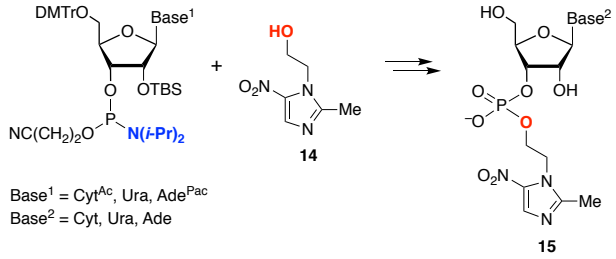
The Raines group developed a hydrophilic cancer prodrug, uridine 3′-(4-hydroxytamoxifen phosphate) (**12**), by using the phosphoramidite method with *N*-methylbenzimidazolium triflate (*N*-MeBIT) (Scheme 4).[30] First, uridine phosphoramidite **9** and 4-hydroxytamoxifen (**10**) were coupled with *N*-MeBIT to afford the corresponding phosphite triester, which was subsequently oxidized to the phosphate **11**. The protecting groups of **11** were cleaved in three steps to afford **12**. The cancer prodrug **12** was activated by human pancreatic ribonuclease (RNase 1) to release



Scheme 4. Chemical synthesis of uridine 3′-(4-hydroxytamoxifen phosphate) (**12**) and its degradation by RNase 1.

the parent drug **10** along with uridine 2′,3′-*O*-cyclic monophosphate (**13**). On the basis of this strategy, Raines and co-workers succeeded in decreasing the proliferation of MCF-7 breast cancer cells.

The Raines group also synthesized a similar prodrug, ribonucleoside 3′-phosphates **15**, from metronidazole (**14**) based on the protocol of Scheme 4 (Scheme 5). When the above prodrug strategy was applied, the release rate of **14** from **15** upon treatment with RNase 1 exhibited increasing dependence on the nucleobase in the order of Cyt > Ura >> Ade.[31] The strategy shown in Schemes 4 and 5 was based on the low specificity for the leaving group in the RNase 1-mediated degradation of ribonucleoside 3′-phosphates.



Scheme 5. Chemical synthesis of ribonucleoside 3′-(metronidazole phosphates) (**15**).

Stec and Baraniak synthesized adenosine 3′,5′-cyclic monophosphorodithioate (*c*AMPS$_2$), an analog of adenosine 3′,5′-cyclic monophosphates (*c*AMP) (Figure 5), for the first time by intramolecular cyclization of adenosine 5′-[*O*-(4-nitrophenyl)phosphoranilidothioate] as a key step.[32] The same group subsequently found that *c*AMPS$_2$ inhibited *c*AMP-induced protein kinase activity.[33] Reese and co-workers cyclized an activated 5′-phosphorodithioate to synthesize *c*AMPS$_2$.[34] By

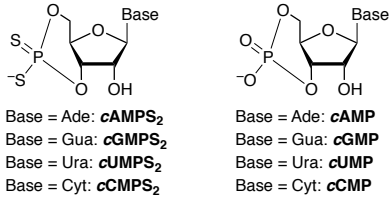
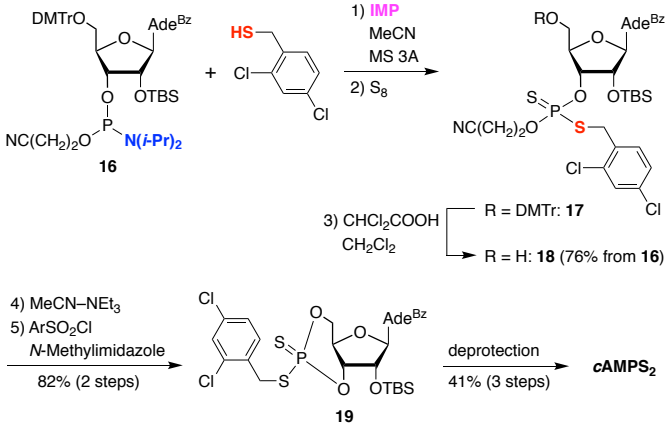


Figure 5. Ribonucleoside 3′,5′-cyclic monophosphorodithioates and ribonucleoside 3′,5′-cyclic monophosphates.

referencing these strategies, we realized a more direct synthesis of *c*AMPS$_2$ using adenosine phosphoramidite **16** as a starting material, as shown in Scheme 6.[35] Phosphoramidite **16** was condensed with (2,4-dichlorophenyl)methanethiol using IMP (Figure 2) as a promoter and the resulting phosphite triester was oxidized with sulfur to give the phosphorodithioate triester **17**. Next, the 5′-*O*-DMTr group of **17** was removed by acid to give **18**. The fully protected cyclic monophosphorodithioate **19** was obtained by removal of the cyanoethyl group on the 3′-phosphate of **18**, followed by intramolecular cyclization of the resulting 3′-phosphodiester using 2,4,6-triisopropylbenzenesulfonyl chloride (ArSO$_2$Cl) and *N*-methylimidazole. Finally, the protecting groups of **19** were cleaved in three steps to afford *c*AMPS$_2$ in an overall yield of 25% from **16**. Other ribonucleoside 3′,5′-cyclic monophosphorodithioates (*c*NMPS$_2$) such as *c*UMPS$_2$, *c*CMPS$_2$, and *c*GMPS$_2$ were similarly synthesized by this method.[36] *c*NMPS$_2$ were found to be more lipophilic than the corresponding



Scheme 6. Synthesis of *c*AMPS$_2$. Ar (in step 5) = 2,4,6-triisopropylphenyl.

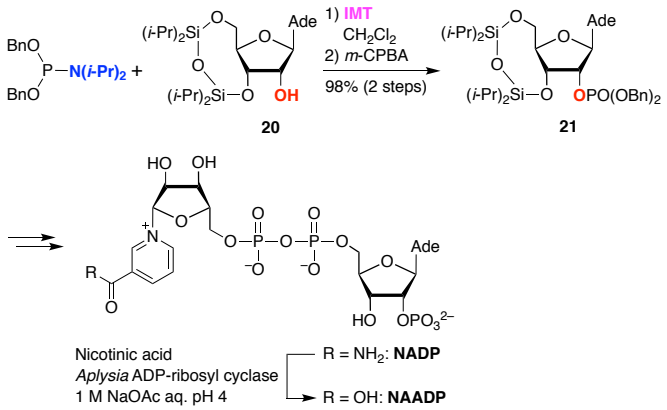
ribonucleoside 3′,5′-cyclic monophosphates (*c*NMP) as judged by the reversed-phase HPLC analysis. In addition, nucleotides with a phosphorodithioate moiety are generally resistant toward enzymes.[37] Moreover, *c*NMP such as *c*AMP[38] and guanosine 3′,5′-cyclic monophosphate (*c*GMP)[39] are involved in various biological events as second messengers in bacteria and eukaryotes. Considering the above properties of *c*NMPS$_2$ and the roles of *c*NMP, *c*NMPS$_2$ are expected to be interesting modified nucleotides.

Synthesis of dinucleotides

Dowden et al. synthesized nicotinamide adenine dinucleotide phosphate (NADP) and nicotinic acid adenine dinucleotide phosphate (NAADP) via 3′,5′-*O*-protected 2′-phosphate **21**, as shown in Scheme 7.[40] Thus, 3′,5′-*O*-protected adenosine **20** was converted to **21** in an excellent yield by treatment of dibenzyl diisopropylaminophosphoramidite and IMT followed by oxidation. Protection of the adenine base was unnecessary, as in the reaction of triol **8** (Scheme 3).

In the early stages of investigation on the porphyrin-modified DNAs by the Stulz group,[41] *N*-phenylimidazolium triflate (*N*-PhIMT) (Figure 6) was employed as a promoter for the phosphoramidite coupling reaction in the solution-phase synthesis of porphyrin-substituted dinucleotides. An outline of this use of *N*-PhIMT was published previously.[42]

The Clivio group synthesized dinucleoside monophosphate **22** containing tetrazolo[1,5-*c*]pyrimidin-5(6*H*)-one aglycon moieties by the phosphoramidite method using IMT and investigated the photosensitized excitation of **22** (Figure 7).[43]



Scheme 7. Synthesis of nicotinamide adenine dinucleotide phosphate (NADP) and nicotinic acid adenine dinucleotide phosphate (NAADP).

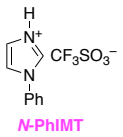


Figure 6. *N*-Phenylimidazolium triflate (*N*-PhIMT).

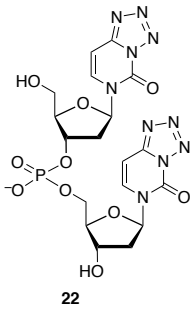
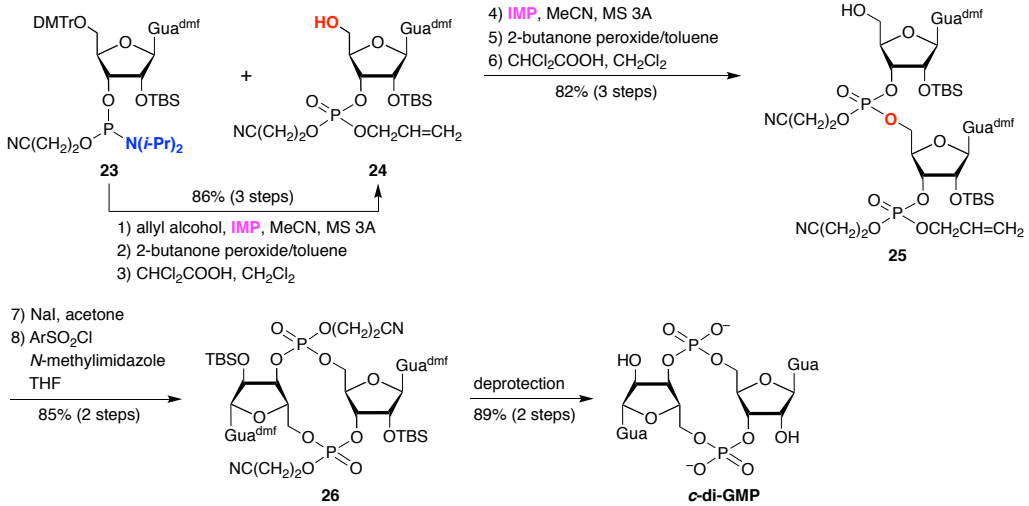
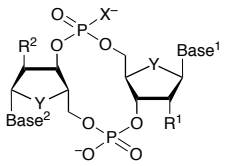


Figure 7. Dinucleoside monophosphate **22** containing tetrazolo[1,5-*c*]pyrimidin-5(6*H*)-one aglycon moieties.



Scheme 8. Synthesis of *c*-di-GMP. Ar (in step 8) = 2,4,6-triisopropylphenyl.

Table 1. *c*-di-GMP analogs synthesized by Hayakawa's method.



Base[1]	Base[2]	R[1]	R[2]	X	Y	Abbrev. or compd. No.	Ref
Gua	Gua	OTBS	OTBS	O	O	2′-OTBS-*c*-di-GMP	47
Gua	Gua	OH	OH	S	O	*c*-GpGps	50
Gua	Ade	OH	OH	O	O	*c*-GpAp	50
Gua	Ino	OH	OH	O	O	*c*-GpIp	50
Gua	Gua	H	OH	O	O	*c*-dGpGp	51
Gua	Ura	OH	OH	O	O	*c*-GpUp	52
Ino	Ino	OH	OH	O	O	*c*-di-IMP	52
Ino	Ura	OH	OH	O	O	*c*-IpUp	52
Ura	Ura	OH	OH	O	O	*c*-di-UMP	52
Ade	Ade	OH	OH	O	O	*c*-di-AMP	53
Ade	Ade	OTBS	OTBS	O	O	2′-OTBS-*c*-di-AMP (**27a**)	53
Ade	Ade	H	H	O	O	*c*-di-dAMP (**27b**)	54
Ade	Ade	OMe	OMe	O	O	**27c**	54
Ade	Ade	F	F	O	O	**27d**	54
Ade[Bz]	Ade[Bz]	OMe	OMe	O	O	**27e**	55
Ade	Ade	OH	OH	O	S	*c*-di-4′-thioAMP	56

Since its discovery as an allosteric activator of a cellulose synthase in *Gluconabacter xylinus*,[44,45] cyclic bis(3′–5′)diguanylic acid (*c*-di-GMP) (Scheme 8) has been widely synthesized and investigated for its unknown biological properties. *c*-di-GMP was enzymatically synthesized from guanosine 5′-triphosphate.[44] Later, van Boom published the first chemical synthesis by the phosphotriester method.[46] However, these two methods cannot provide adequate amounts of *c*-di-GMP for the investigation of its various biological activities. To overcome this problem, Hyodo and Hayakawa developed a more practical method, in which IMP played an important role as a promoter in the phosphoramidite coupling reactions, as shown in Scheme 8.[47] First, guanosine cyanoethyl phosphoramidite **23** was converted to nucleotide **24** by condensation with allyl alcohol in the presence of IMP, oxidation with 2-butanone peroxide, and removal of the 5′-*O*-DMTr group. Next, this three-step procedure was employed for coupling phosphoramidite **23** and nucleotide **24** to afford the linear dimer **25**. The fully protected *c*-di-GMP **26** was obtained by removal of the allyl group of **25**, followed by intramolecular cyclization of the resulting 3′-phosphodiester. Finally, removal of the protecting groups of **26** afforded *c*-di-GMP. By using the synthesized *c*-di-GMP, several new biological activities of *c*-di-GMP were discovered, such as the regulation of biofilm formation and infection of host cells by various bacteria, and the activation of immune response.[48,49]

This method has been further applied to the synthesis of various *c*-di-GMP analogs. These include *c*-GpGps, *c*-GpAp, *c*-GpIp,[50] *c*-dGpGp,[51] *c*-di-UMP,[52] *c*-di-AMP,[53] 2′-modified-*c*-di-AMPs **27**,[53–55] and *c*-di-4′-thioAMP[56] (Table 1). Endo-S-*c*-di-GMP (Figure 8) was also synthesized via IMP-promoted phosphoramidite coupling reactions, although a different cyclization method, i.e., phosphorothioate–iodide macro-ring closure, was employed.[57]

Shortly after Hyodo and Hayakawa reported the synthesis of

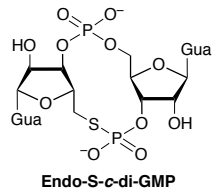


Figure 8. Endo-S-*c*-di-GMP.

c-di-GMP,[47] Jones disclosed another versatile and scalable method via the phosphoramidite coupling followed by fast ring closure using the *H*-phosphonate approach.[58] For recent progress on the synthetic and biological investigations of cyclic dinucleotides, please refer to the relevant reviews.[59–63]

Synthesis of trinucleotides

The Strobel group synthesized a ribosomal P-site substrate, CCA-pcb (cytidylyl-(3′–5′)-cytidylyl-(3′–5′)-3′(2′)-*O*-(*N*-(6-D-

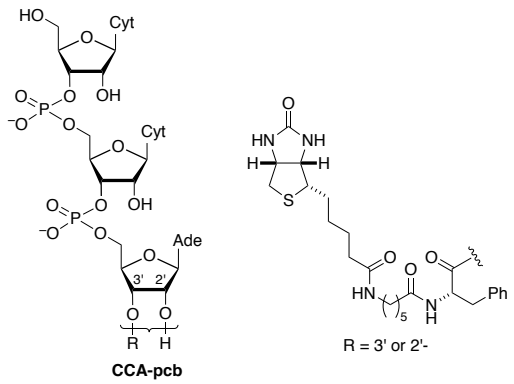
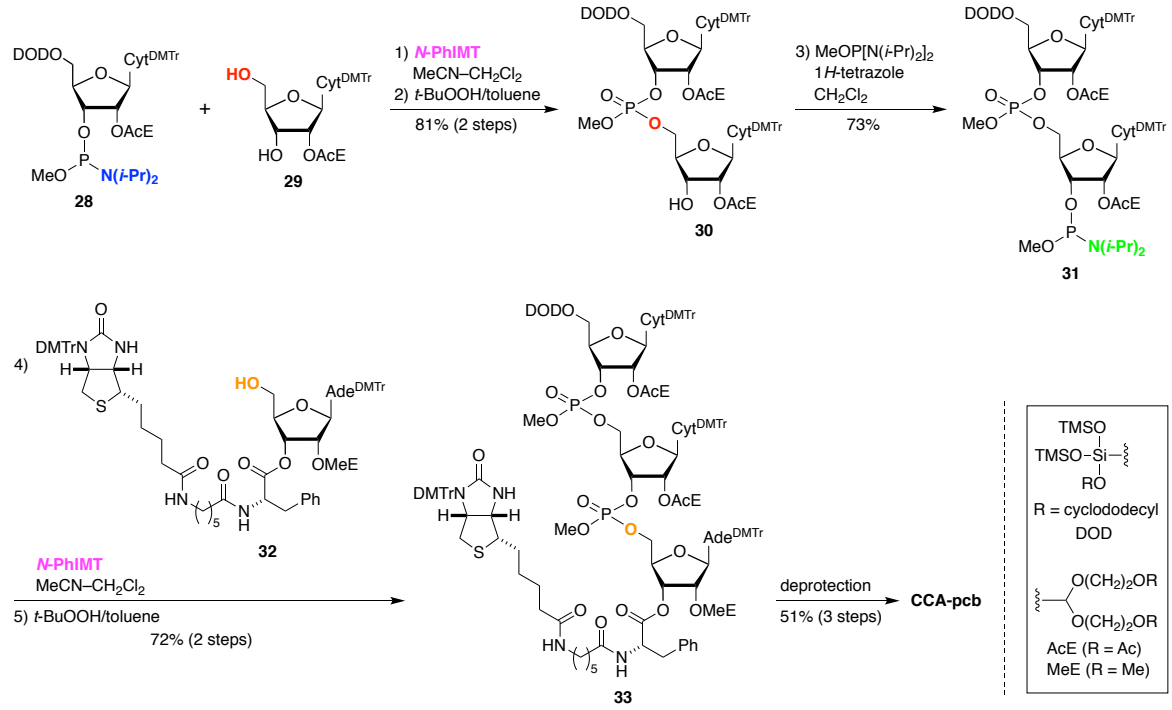


Figure 9. CCA-pcb.

(+)-biotinoylaminohexanoyl)-L-phenylalanyl)adenosine) (Figure 9), by using phosphoramidite coupling reactions promoted by *N*-PhIMT (Figure 6) as key steps.[64] The essence of the synthesis is shown in Scheme 9. A combination of the bis(trimethylsiloxy)cyclododecyloxylsilyl (DOD) group at the 5′-terminus, methyl groups at the phosphates, and acid-labile DMTr, bisacetoxyethoxymethyl (AcE), and bismethoxyethoxymethyl (MeE) groups at other functional sites is essential to avoid the breakage of the ester linkage at the 3′- or 2′-terminus. Coupling of phosphoramidite **28** and 3′,5′-nonprotective nucleoside **29** with *N*-PhIMT followed by oxidation with *tert*-butyl hydroperoxide afforded dinucleoside phosphate **30** selectively, which was phosphitylated to give **31**. The second coupling reaction between **31** and adenosine-pcb fragment **32** with *N*-PhIMT followed by oxidation gave the fully protected CCA-pcb **33**. Removal of the protecting groups gave CCA-pcb. Use of 1*H*-tetrazole and 5-ethylthio-1*H*-tetrazole in the coupling reactions provided moderate yields of **30** and traces of **33**. On the basis of this approach, the Strobel group synthesized various isotopomers of CCA-pcb to gain insights into the mechanism of the ribosome-catalyzed reactions.[65]



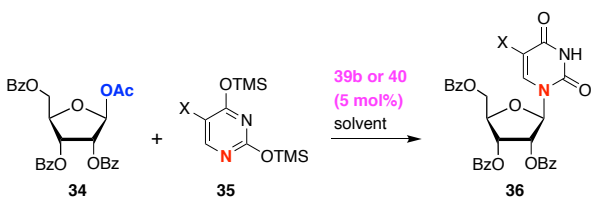
Scheme 9. Synthesis of CCA-pcb.

Acidic oxazolium salts and acidic thiazolium salts

Lewis acids such as trimethylsilyl triflate (TMSOTf) and tin tetrachloride are known to promote Vorbrüggen *N*-glycosylation reactions (cf. Scheme 10).[66,67] In 2011, the Jamison group demonstrated that acidic pyridinium salt **37a** as a Brønsted acid (Figure 10) catalyzed the reactions.[68] The anomeric acetate of the glycosyl donor **34** might be protonated by a Brønsted acid to form a sugar cation and acetic acid, which is a key step for the initiation of the *N*-glycosylation. Therefore, stronger Brønsted acids would be more reactive.

To confirm the above assumption, catalytic activities of acidic azolium and pyridinium salts shown in Figure 10 having various pK_a values were evaluated in the reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**34**) and silylated 5-fluorouracil **35a** in either acetonitrile or acetone under refluxing conditions (cf. Scheme 10).[18] Screening of the salts revealed that the perchlorates showed higher reactivity than the corresponding triflates. In addition, the reactivity increased as the parent nitrogen heterocycle was changed from the imidazole derivative to the pyridine, thiazole, and oxazole derivatives, which supported the above assumption. Among the salts investigated, 2-methyl-5-phenylbenzoxazolium perchlorate (**39b**)[69] was the most active and its activity was higher than those of TMSOTf and tin tetrachloride. On the basis of this result, a solid-supported acidic oxazolium perchlorate **40** was prepared as a heterogeneous catalyst. The catalytic activity was comparable to that of **39b**.[19] Oxazolium salt **39b** or **40** catalyzed reactions with silylated uracils **35** having an electron withdrawing group (Scheme 10).[70] On the other hand, a reaction with silylated thymine **35g** having an electron donating group in the presence of **40** was quite slow, and starting materials remained after 6 h. To complete the reaction, higher temperature (140 °C) and ~~more~~ longer time were necessary. This condition with **40** at 140 °C was also applicable to a reaction with silylated N^6-benzoyladenine to give N^6,2′,3′,5′-tetra-*O*-benzoyladenosine in 88% yield.

Solid-supported salt **40** catalyzed *N*-glycosylations employing tetra-*O*-acetyl-β-D-ribofuranose (**41**) and pentaacetyl-β-D-glucose (**43**) as glycosyl donors to give the *N*-glycosylated products in high yields (Scheme 11).[19] Increased catalyst loading was necessary in the reaction of **43**, which had lower reactivity than ribofuranose **41**.



Scheme 10. Standard *N*-glycosylation reactions.

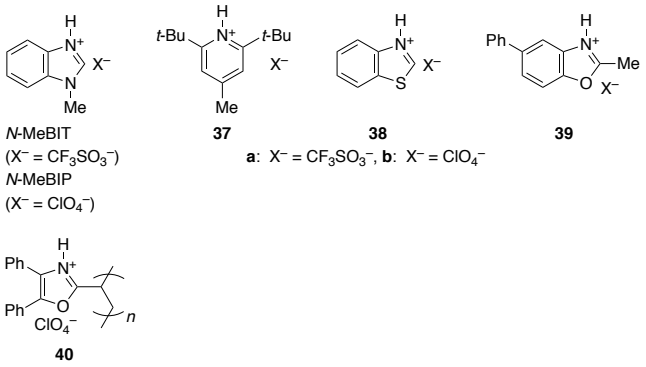
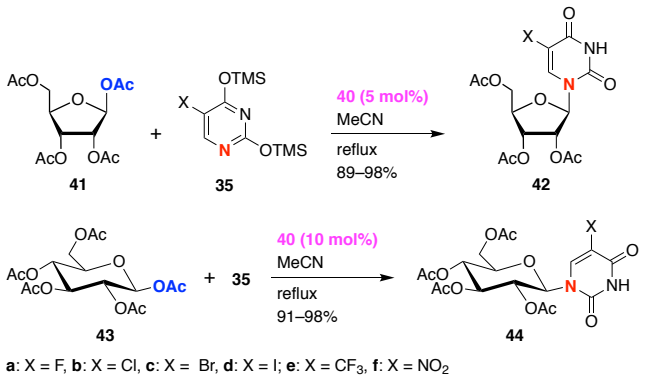
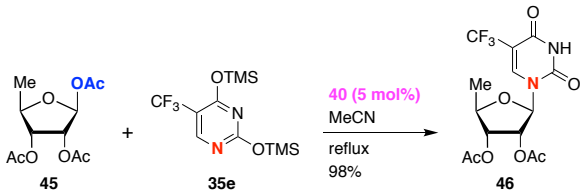


Figure 10. Acidic 1,3-azolium and pyridinium salts.



Scheme 11. Synthesis of pyrimidine nucleosides.

Catalyst reusability was examined in the reaction of 1,2,3-tri-*O*-acetyl-5-deoxy-β-D-ribofuranose (**45**) and silylated 5-(trifluoromethyl)uracil **35e** (Scheme 12).[19] *N*-Glycosylated product **46** was obtained in 98% yield in the presence of 5 mol% of **40**. The recovered polymer showed no catalytic activity, leaving **45** and 5-(trifluoromethyl)uracil intact. This suggests that **40** lost a proton in the course of the reaction with the liberation of acetic acid and that trimethylsilyl perchlorate formed in situ catalyzed the production of **46**. Consistent with this speculation, the recovered polymer activated with perchloric acid was successfully used as a catalyst.



Scheme 12. Standard *N*-glycosylation reaction for investigating catalyst reusability.

Conclusion

One of the important factors for the applications of acidic 1,3-azolium salts is Brønsted acidity. A subset of acidic imidazolium salts that are compatible with the DMTr group promote phosphoramidite coupling reactions in a stoichiometric manner. The salts are effective for reactions using sterically bulky phosphoramidite building blocks such as those having a 2′-*O*-TBS or 5′-*O*-DOD protector. In addition, IMT is advantageous for the coupling reactions in the presence of an unprotected adenine or guanine base. On the other hand, more acidic thiazolium and oxazolium salts cannot be applied for the above coupling reactions because of their strong acidities.[71,72] Instead, these salts promote Vorbrüggen-type *N*-glycosylation reactions catalytically. A combination of the substituted benzoxazole and perchloric acid shows high catalytic activity, which enables the development of the corresponding solid-supported oxazolium salt. Moreover, selection of substituents and counter anions of acidic 1,3-azolium salts is important to obtain non-hygroscopic salts, which can be used as highly active reagents. Reactions promoted by acidic 1,3-azolium salts are key steps for the synthesis of various important nucleosides and nucleotides. It is noted that each acidic 1,3-azolium salt should be used *in a complementary fashion*. There is great potential for further progress of acidic thiazolium and oxazolium salts in organic synthesis. Efforts to expand the application of these intriguing promoters are currently underway in our laboratories.

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