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Expeditious oligosaccharide synthesis via selective, semi-orthogonal, and orthogonal activation

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Abstract

Traditional strategies for oligosaccharide synthesis often require extensive protecting and/or leaving group manipulations between each glycosylation step, thereby increasing the total number of synthetic steps while decreasing the efficiency of the synthesis. In contrast, expeditious strategies allow for the rapid chemical synthesis of complex carbohydrates by minimizing extraneous chemical manipulations. Oligosaccharide synthesis by selective activation of one leaving group over another is one such expeditious strategy. Herein, the significant improvements that have recently emerged in the area of the selective activation are discussed. The development of orthogonal strategy further expands the scope of the selective activation methodology. Surveyed in this article, are representative examples wherein these excellent innovations have been applied to the synthesis of various oligosaccharide sequences.

Keywords

Oligosaccharides; selective activation; strategy; orthogonality; glycosylation

1 Introduction. Chemical glycosylation and conventional oligosaccharide synthesis

Carbohydrates are the most abundant biomolecules on Earth, nevertheless, their chemistry and biology has been a relatively slowly developing field. To ensure the availability of pure complex carbohydrates, their chemical^{1,2} or enzymatic^{3,4} synthesis has become the topic of prime importance. The development of stereoselective methods and efficient strategies for the synthesis of complex carbohydrates has become critical to the emerging areas of glycosciences. The monomeric units in oligosaccharides are connected via O-glycosidic linkages. The glycosidic linkage is obtained by means of the glycosylation reaction that is commonly based on the nucleophilic displacement of the anomeric leaving group (LG) of the glycosyl donor with a hydroxyl moiety of the glycosyl acceptor (Scheme 1). The remaining hydroxyls of both units are typically masked with temporary protecting groups (P). The achievement of high yields and complete stereocontrol is difficult due to the complexity of the glycosylation process that often proceeds along with a variety of side

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Dedicated to Prof. Dr. András Lipták on the occasion of his 75th birthday

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reactions.^{5,6} However, a single-step glycosylation is not the only challenge researchers working on oligosaccharide synthesis face. Traditional linear approaches for the synthesis of oligosaccharides imply conversion of the disaccharide into second-generation glycosyl donors or acceptors. This transformation typically involves protecting group manipulations or leaving group installation between each glycosylation step (Scheme 1). Such additional manipulations increase the number of total synthetic steps and decrease the efficiency of the oligosaccharide assembly as reflected in dramatic drop in yield. This called for revisiting existing linear strategies for oligosaccharide synthesis and some significant improvements have already emerged.⁷

2. Expeditious oligosaccharide synthesis: concepts of selective and chemoselective activations

Recent strategies for oligosaccharide synthesis are typically based on the direct multi-step activation of a series of building blocks.^{7,8} These expeditious approaches significantly shorten oligosaccharide assembly by minimizing the need for protecting group manipulations between glycosylation steps. Nicolaou's selective activation,⁹ Fraser-Reid's armed-disarmed approach,¹⁰ Danishefsky's glycal assembly,¹¹ Ogawa's orthogonal technique,^{12,13} Roy's¹⁴ and Boons'¹⁵ active-latent concept, Wong's and Ley's programmable strategies,^{16–19} are only few such strategies to mention. One of the most conceptually attractive and practically efficient procedures, Fraser-Reid's *armed-disarmed approach*, is based on the principle of chemoselectivity. According to this principle, a benzylated (electronically activated, armed) glycosyl donor is chemoselectively activated over the acylated (electronically deactivated, disarmed) glycosyl acceptor bearing the same leaving group (Scheme 2).^{20,21}

The availability of a suitable mild promoter is essential to effectively differentiate the reactivity levels of the armed and disarmed species. At this stage, a 1,2-*cis*-linked disaccharide is preferentially obtained due to the general use of the ether-type arming substituent, a non-participating group. The obtained disaccharide can then be used for 1,2-*trans* glycosylation directly in the presence of a more potent promoter that can activate the disarmed leaving group. Initially developed for *O*-pentenyl glycosides,^{21,22} this approach works with many other classes of stable glycosyl donors.^{7,23} The traditional armed-disarmed strategy thus offers an efficient tool for the synthesis of oligosaccharides with *cis-trans* glycosylation sequences.

In principle, the use of the selective activation concept offers a more flexible oligosaccharide assembly because this approach does not rely on the nature of the protecting groups. Instead, it requires a few leaving groups (LG^a, LG^b, LG^c, etc., Scheme 3) that can be sequentially activated. Unfortunately, the application of this relatively simple concept to large oligosaccharide is still limited, so is the number of leaving groups compatible with the principle of sequential activation. This in part can be addressed by related semi-orthogonal and orthogonal strategies (vide infra).

This chapter is dedicated to a thorough overview of strategies making use of the principle of selective activation of one leaving group of another. The accumulated knowledge has translated into more advanced semi-orthogonal and orthogonal strategies that are also discussed below. Other general concept for oligosaccharide synthesis involves two-step activation or pre-activation. This approach allows for using the same leaving group in both donor and acceptor counterparts and since this approach is practically independent on the nature of the protecting groups used, a selective approach-like flexibility can be achieved. Due to the scope of this review, the two-step activations and pre-activation-based protocols

will not be thoroughly discussed. The reader is referred to the original literature, which is rather abundant and is not limited to the references listed.^{24–26}

3 Selective activation

3.1 Glycosyl chlorides, bromides, and iodides

Being relatively unstable derivatives, glycosyl chlorides and bromides can be selectively activated over other, more stable leaving groups, including thio, seleno and *n*-pentenyl glycosides. The first application of glycosyl bromides in selective activation strategy was reported in 1973. Zen *et al.*²⁷ demonstrated that glycosyl bromide donor can be selectively activated over a thioglycoside acceptor in the presence of silver carbonate (AgCO₃). Herein this principle is illustrated by a more recent example of a two-step synthesis reported by Lönn (Scheme 4).^{28,29} Accordingly, fucosyl bromide **1** was selectively activated over the *S*-ethyl glycosyl acceptor **2**. The resulting disaccharide **3** was then coupled directly with acceptor **4** in the presence of MeOTf to afford trisaccharide **5**. This example clearly illustrates the advantage of the selective activation strategy over the traditional approach that would imply additional protecting/leaving group manipulations after the first coupling step.

Stronger promoters for bromide activation, such as AgOTf, can be also successfully employed in selective activations over thioglycosides.^{30,31} For example, as reported by Oscarson *et al.*, the synthesis of a tetrasaccharide of *Vibrio cholerae* O139 began with AgOTf-promoted activation of glycosyl bromide **6** over *S*-ethyl acceptor **7** (Scheme 5).³² The resulting disaccharide **8** was then subjected to deprotection (like in conventional strategy) and the resulting diol **10** was glycosylated with glycosyl bromide **11** to afford tetrasaccharide **12**. All three glycosidic linkages were constructed using selective activation strategy although some interim protecting group manipulations were necessary.

Kovac *et al.* showed that glycosyl bromides and chlorides can be selectively activated with AgOTf in presence of the anomeric acetate.³³ Pinto *et al.* reported selective activation of glycosyl bromide donors over phenyl selenoglycoside acceptors, which was realized in the presence of AgOTf and γ -collidine.³⁴ Selective activation of glycosyl bromide over *n*-pentenyl glycoside acceptor in presence of AgOTf was demonstrated during the synthesis of an elicitor-active analog³⁵ and in the synthesis of glycosylphosphatidylinositol.³⁶ Mukaiyama and Kobashi introduced tri(1-pyrrolidino)phosphine oxide as an activator for glycosyl bromide suitable for conducting selective activations.³⁷ The activation takes place via glycosyl phosphonium bromide intermediate. Scheme 6 illustrates the activation of glycosyl bromide **13** over thioglycoside **14** and glycosyl fluoride **15** leading to the respective disaccharides **16** and **17** in good yields.

Glycosyl chlorides can be also selectively activated with AgOTf in presence of thioglycosides.³⁸ For example, this type of activation was employed in the synthesis of dodecasaccharide described by Ito *et al.*^{39,40} Selective activation of glycosyl chloride over glycosyl fluoride was also employed in activation of sialyl donor **18** over acceptor **19** to afford 2→8-linked disialoside **20** in 49% yield (Scheme 7).^{41,42}

Gervay-Hague *et al.* described the selective activation of glycosyl iodide **21** over glycosyl acceptor **22** equipped with the anomeric acetate under neutral conditions (TBAI/DIPEA, Scheme 8).^{43,44} Oscarson *et al.*⁴⁵ activated iodide donor **21** over thioglycoside acceptor **24** in the presence of triphenylphosphine oxide (Ph₃PO) to afford the corresponding disaccharide **25**.

3.2 Glycosyl fluorides

Glycosyl fluorides⁴⁶ are very versatile building blocks because they can be used both as glycosyl donors and glycosyl acceptors in selective activations. Nicolaou and his co-workers showed that glycosyl fluorides can be activated in the presence of thioglycosides with AgClO_4 and SnCl_2 . An example of the total synthesis of the tumor-associated Le^x morif involving such principle is depicted in Scheme 9.⁴⁷

As shown in Scheme 10, a similar concept was applied to the synthesis of tetrasaccharide **33** containing two sialic acid units, which were also connected by selective activation (*vide supra*). Thus, the activation of glycosyl fluoride donor **20** (see Scheme 7) over thioglycoside acceptor **32** was achieved in presence of AgOTf/SnCl_2 and resulted in the formation of tetrasaccharide **33**.^{41,42}

In 2002, Mukaiyama *et al.* reported that a catalytic amount of protic acid, such as TfOH , HClO_4 or $\text{C}_4\text{F}_9\text{SO}_3\text{H}$ is also suitable for the activation of fluoride donors over thioglycoside acceptors.⁴⁸ Danishefsky demonstrated that glycals also can tolerate activation of glycosyl fluoride in the presence of Sn(OTf)_2 .^{49,50} Nicolaou and co-workers have described a related glycosylation strategy based on two-stage activation concept, whereby thioglycoside is first converted into a glycosyl fluoride, which is then used as a glycosyl donor for coupling with a thioglycoside acceptor.^{24,51}

3.3 O-Leaving groups

3.3.1 Hemiacetals (1-OH derivatives)—The direct activation of 1-hydroxyl glycosyl donors is undoubtedly the most direct method of glycosylation as it does not require the use of a formal leaving group.⁵² In 1976, Leroux and Perlin developed the direct dehydrative glycosylation using triflic anhydride in the presence of a sterically hindered base, γ -collidine, and Bu_4NBr .^{53,54} The reaction proceeded via a stepwise activation of glycosyl donor **34** via the formation of the anomeric triflate and bromide intermediates. Resultantly, glycosylation of glycosyl acceptor **35** bearing an anomeric acetate group afforded disaccharide **36** in 60% yield (Scheme 11a). In the recent years, Gin and co-workers have developed a sulfonium-based electrophilic activation of hemiacetal donor via the activated anomeric oxosulfonium intermediate by the treatment with Ph_2SO and Tf_2O .⁵⁵ Van der Marel *et al.* utilized the diphenyl sulfoxide protocol for selective glycosylation of hemiacetal with thioglycosides.^{56,57} Thus, $\text{Ph}_2\text{SO/Tf}_2\text{O}$ -mediated dehydrative condensation of hemiacetal donor **37** with thioglycoside **38** afforded disaccharide **39** in 91%. This approach was then extended to the synthesis of a heparin oligosaccharide (*vide infra*).⁵⁷

3.3.2 Acyl and carbonyl derivatives—In general, Lewis acids (SnCl_4 , FeCl_3 , $\text{BF}_3\text{-OEt}_2$, TsOH) are used as promoters to activate glycosyl esters and carbonates.⁵² Mukaiyama *et al.* utilized a preactivation-based glycosidation of glycosyl acetate **40** using iodotrimethylsilane followed by the addition of thioglycoside glycosyl acceptor **41** and phosphine oxide (Scheme 12a).⁵⁸ Another example involves selective activation of anomeric carbonate **43** over thioglycoside **44** in the presence of $\text{TrB(C}_6\text{F}_5)_4$ (Scheme 12b).^{59,60} Recently, Yu *et al.* introduced *o*-alkynylbenzoates as efficient glycosyl donors, which can be activated with catalytic amount of Ph_3PAuOTf .^{61,62} The utility of glycosyl donor **46** was demonstrated by selective activation over thioglycoside acceptor **47** to afford the disaccharide **48** (Scheme 12c).⁶¹

3.3.3. O-Imidates—Glycosyl trichloroacetimidates, which over the years have become the most commonly used glycosyl donors, were introduced by Schmidt and co-workers.⁶³ The selective activation of trichloroacetimidates over other glycosyl donors can be straightforwardly executed with TMSOTf ⁶⁴ or $\text{BF}_3\text{-OEt}_2$.⁶⁵ For example, as a part of the

synthesis of glycolipid of *Mycobacterium smegmatis*, TMSOTf-promoted coupling of trichloroacetimidate **49** and thioglycoside acceptor **50** afforded $\beta(1\rightarrow4)$ linked trisaccharide **51** in 71% yield (Scheme 13a).⁶⁴

Pinto *et al.* showed that glycosyl trichloroacetimidate donor can be activated with TESOTf over selenoglycoside acceptor.³⁴ A number of syntheses involving the activation of trichloroacetimidates over *n*-pentenyl glycosides also emerged.^{66–68} For example, trichloroacetimidate glycosyl donor **52** was selectively activated over with *n*-pentenyl glycosyl acceptor **53** in the presence of TESOTf (Scheme 13b).⁶⁷ Recently, Mukhopadhyay *et al.* showed that H₂SO₄-silica can be used to activate trichloroacetimidate **55** over propargyl glycosyl acceptor **56** leading to trisaccharide **57** in 91%.⁶⁹

Similar glycosyl donors, (*N*-phenyl)trifluoroacetimidates introduced by Yu can also be selectively activated over a range of glycosyl acceptors bearing stable anomeric leaving groups.⁷⁰ As reported by Seeberger *et al.*⁷¹ activation of (*N*-phenyl)trifluoroacetimidate **58** over *n*-pentenyl glycosyl acceptor **59** was accomplished in the presence of TMSOTf (Scheme 14a). Iadonisi *et al.* determined that the reactivity of glycosyl trichloro- and (*N*-phenyl)trifluoroacetimidates can be differentiated.⁷² It was found that a mild promoter, such as Yb(OTf)₃, allows for selective activation of glycosyl trichloroacetimidate building block **61** over glycosyl (*N*-phenyl)trifluoroacetimidate **62** (Scheme 14b). The resulting disaccharide is then coupled with glycosyl acceptor **63** in a one-pot manner. This was affected by using additional quantities of the promoter and led to the formation of trisaccharide **64** in 40% yield over two steps.

Mukaiyama and co-workers reported selective activation of cyclic O-imidate donor, 6-nitro-2-benzothiazole **65** over thioglycoside **66** or glycosyl fluoride acceptor **15**.⁷³ As depicted in Scheme 15, HB(C₆F₅)₄-catalyzed selective activations resulted in the formation of disaccharides **67** and **68**, respectively, in good yields. Glycosyl thioformimidates can be activated over fluorides and thioglycosides in the presence of catalytic amount of protic and Lewis acid.⁷⁴

3.3.4 O-P derivatives—Several glycosyl donors possessing an O-P anomeric motif have been investigated.⁷⁵ Diethyl and dibenzyl glycosyl phosphites independently introduced by Schmidt⁷⁶ and Wong,⁷⁷ respectively, require only catalytic amount of TMSOTf (usually 10–20%), which allows for their selective activations over a range of leaving groups. For example, the coupling of sialyl phosphite donor **69** and thioglycoside acceptor **70** was accomplished using TMSOTf.⁷⁸ Also demonstrated that the coupling of glycosyl phosphites with glycals can be affected in the presence of TMSOTf.⁷⁹ Further expansion emerged with the development of glycosyl diphenyl phosphates,⁸⁰ diphenylphosphineimides,⁸¹ and phosphoroamidates.⁸² Towards the synthesis of ganglioside GM3, sialyl phosphite **72** could be selectively activated over phosphorodiamidate acceptor **73** in the presence of TMSOTf, BF₃·OEt₂ or TfOH (Scheme 16b).⁸³

Seeberger and co-workers expanded the use of glycosyl phosphates as glycosyl donors.^{84,85} TMSOTf, TBSOTf, or BF₃·OEt₂ were proved to be suitable promoters for selective activation of glycosyl phosphates. For example, selective activation of phosphate **75** over thioglycoside acceptor **76** in the presence of TMSOTf resulted in the formation of disaccharide **77** in 96% yield (Scheme 17a). Similarly, glycosyl phosphate **78** was activated over *n*-pentenyl acceptor **79** that resulted in the formation of disaccharide **80** in 82% yield (Scheme 17b). Mukaiyama *et al.* introduced glycosyl diphenylphosphinites as a glycosyl donors that can be activated over thioglycoside and fluoride acceptors in the presence of MeI.⁵⁸

3.3.5 Transglycosylation (*n*-pentenyl, propargyl, and hetaryl glycosides as glycosyl donors)—*n*-Pentenyl glycosides introduced by Fraser-Reid⁸⁶ can be activated with an electrophilic reagent, most commonly IDCP, NIS/TfOH or NIS/TMSOTf. Since these are essentially the same activation conditions as those for the activation of common thioglycosides, the use of *n*-pentenyl glycosides as glycosyl donors in selective activations is rare. Although *n*-pentenyl glycoside **81** could be selectively activated with IDCP over thioglycoside **82** (Scheme 18a)⁸⁷ this coupling required the enforcement by the electronic effects. Resultantly, only armed *n*-pentenyl glycosides could be activated over the disarmed thioglycosides. Lopez *et al.* demonstrated that *n*-pentenyl glycosides can be selectively activated over glycosyl fluoride acceptors (vide infra).⁸⁸ More recently, Hotha *et al.* observed that *n*-pentenyl glycoside **84** could be activated over propargyl glycosyl acceptor **85** in the presence of NIS/TMSOTf (Scheme 18b).⁸⁹

The utility of 3-methoxy-2-pyridyl glycoside as a glycosyl donor in selective glycosylations was described by Hanessian *et al.*⁹⁰ As depicted in Scheme 19a, donor **87** was selectively activated over thioglycoside **88** in the presence of Cu(OTf)₂. Very recently, Hotha described that propargyl glycoside **90** can be selectively activated over *n*-pentenyl glycoside **91** in the presence of AuBr₃ at 65°C.⁸⁹ As depicted in Scheme 19b, disaccharide **92** was isolated in 65 % yield. Chenault *et al.* discovered that isopropenyl glycosides can be activated over *n*-pentenyl glycosides in the presence of TMSOTf.⁹¹ Jensen and co-workers reported a glycosylation method employing methyl 2-hydroxy-3,5-dinitrobenzoate glycosides (methyl 3,5-dinitrosalicylate, DISAL) as a glycosyl donors.⁹² DISAL glycosyl donor could be selectively activated over thioglycoside acceptor in the presence of LiClO₄ and Li₂CO₃ as the promoter system.⁹³ Kim *et al.* discovered that 2-(benzyloxycarbonyl)benzyl (BCB) glycosides are perfectly stable, whereas the corresponding 2-(hydroxycarbonyl)benzyl (HCB) counterparts can be activated in presence of Tf₂O and DTBMP.⁹⁴ This phenomenon was applied to selective activation of 2-(hydroxycarbonyl)benzyl donor over 2-(benzyloxycarbonyl)benzyl acceptor. This activation, however, was performed using pre-activation conditions under which HCB was first treated with DTBMP (30 min), followed by the treatment with Tf₂O. After that, BCB glycosyl acceptor was added, therefore, formally this cannot be classified as the selective activation.

3.4 S-Leaving groups

3.4.1 Sulfoxides, thiocyanates, xanthates, etc—Glycosyl sulfoxides prepared from the corresponding thioglycosides via oxidation,⁹⁵ can be glycosidated in the presence of trifluoromethanesulfonic anhydride.^{96,97} In 1994, van Boom *et al.* reported that TMSOTf and triethylphosphite (TEP) is an effective promoter system for the selective activation of phenylsulfenyl glycosides over phenylthio glycoside acceptors.⁹⁸ The synthesis of antigens Le^a, Le^b and Le^x utilizing the glycosyl sulfoxide method was reported by Kahne (Scheme 20).⁹⁹ Thus, glycosidation of sulfoxide **93** in the presence of Tf₂O and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) over S-phenyl glycoside **94** resulted in the formation of disaccharide **95** in 86% yield. The latter was converted into a glycosyl acceptor **96**, which was subjected to another round of selective glycosylation with glycosyl sulfoxide **97**. The resulting trisaccharide **98** was obtained in 95% yield.

Kochetkov and co-workers showed that glycosyl thiocyanates can be selectively activated over thioglycoside acceptors.¹⁰⁰ As depicted in Scheme 21a, thiocyanate **99** was selectively activated over 6-*O*-tritylated thioglycoside **100** in the presence of triphenylmethylm perchlorate (TrClO₄) as an activator. Fügedi *et al.* introduced glycosyl 1-piperidinecarbodithioates as glycosyl donors that can be activated in the presence of AgOTf or TMSOTf.¹⁰¹ As depicted in Scheme 21b, selective activation of 1-piperidinecarbodithioate donor **102** over thioglycosides acceptor **103** was affected in the

presence of AgOTf and resulted in the formation of disaccharide **104**. Along similar lines, condensation of pentafuranosyl dithiocarbamate with 5-nitro-2-pyridyl thioglycoside in the presence of NIS/TfOH was described by Bogusiak and Szeja.¹⁰²

3.4.2 Thioimides—The first wave of glycosyl thioimides, compounds with a generic leaving group $\text{SCR}^1=\text{NR}^2$, included benzothiazolyl,¹⁰³ pyridin-2-yl,^{104–106} pyrimidin-2-yl,^{104,107} imidazolin-2-yl,¹⁰⁴ and 1'-phenyl-1*H*-tetrazolyl.¹⁰⁸ Although all of these derivatives have been tested as glycosyl donors and promising results have been obtained, the application of this class of compounds to selective activations emerged later. A few years ago, Demchenko *et al.* found that *S*-benzoxazolyl (SBox)¹⁰⁹ and *S*-thiazolynyl (STaz) glycosides¹¹⁰ can be selectively activated over other classes of leaving groups. For example, AgBF₄ – promoted activation of SBox glycoside **105** over *n*-pentenyl glycoside acceptor **106** resulted in the formation of disaccharide **107** in 86% yield (Scheme 22a).¹¹¹ De Meo and Parker described that SBox sialyl donor **108** can be activated over SET glycosyl acceptor **109** in the presence of AgOTf (Scheme 22b).¹¹²

STaz glycosyl donor **111** was glycosidated selectively over thioglycoside acceptor **112** in the presence of AgBF₄ (Scheme 23a).¹¹¹ SBox glycosyl donor **114** could be selectively activated over STaz acceptor **115** in the presence of Bi(OTf)₃ to afford disaccharide **116** in 69% yield (Scheme 23b).¹¹³

3.4.3 S-Alkyl and S-aryl glycosides—Alkyl and aryl thioglycosides have been widely studied as versatile glycosyl donors for oligosaccharide synthesis.^{114–116} As has been demonstrated by a number of examples (*vide supra*), thioglycosides can act as glycosyl acceptors. These properties make thioglycosides suitable building blocks for the use in a broad variety of concepts for oligosaccharide synthesis including chemoselective, selective and iterative glycosylations. As shown by Ogawa *et al.*, selective activation of thioglycosides over glycosyl fluorides can be executed in the presence of NIS and AgOTf as a promoter system.¹² In addition, other promoters including NIS/TfOH,⁴⁰ MeOTf,^{39,117} and DMTST^{118,119} are also capable of the selective activation of thioglycosides over fluorides. For example, selective activation of thioglycoside **117** over fluoride acceptor **118** in the presence of DMTST led to the formation of trisaccharide **119** in 85% yield (Scheme 24a).¹¹⁹ Selective activation of thioglycoside **120** over *S*-thiazolynyl glycosyl acceptor **115** could be affected in the presence of NIS and catalytic TfOH (Scheme 24b).¹¹⁰ Boons reported that the glycosidation of thioglycoside **121** with di-*O*-trityl pentenyl glycosyl acceptor **122** can be achieved in the presence of MeOTf (Scheme 24c).¹²⁰ The unusual regioselectivity obtained here is due to the observation reported by Kochetkov *et al.* that trityl ethers reverse the reactivity of alcohols towards glycosylation.¹²¹ Boons and co-workers also demonstrated that the increase of steric hindrance around the active site of the leaving group has a dramatic effect on the leaving group ability.¹²² Thus, it was shown that an *S*-ethyl glycoside can be selectively activated over dicyclohexylmethyl thioglycoside in the presence of NIS/TMSOTf at low temperature.

Ensley demonstrated that the activation of thioglycosides over 1-*O*-acyl glycosyl acceptor can be performed in the presence of NIS/AgOTf.¹²³ It was also reported that glycals are stable under MeOTf-promoted activation of thioglycosides.¹²⁴ Recently, it was reported that *S*-tolyl donor **124** can be selectively activated over propargyl glycosyl acceptor **125** in the presence of NIS/H₂SO₄-silica.⁶⁹ As shown in Scheme 25, the resulting disaccharide **126** (obtained in 87% yield) was converted into glycosyl acceptor **127** and then subjected to glycosylation with *S*-tolyl glycosyl donor **128** under the same reaction conditions.

3.5 Other classes of glycosyl donors

Anomeric phenylseleno glycosides introduced by Pinto *et al.* are very effective glycosyl donors that can be selectively activated over thioglycosides with AgOTf and K₂CO₃.^{34,125} Selenoglycosides are also more reactive towards MeOTf or NIS/TfOH than their thioglycoside counterparts.^{126,127} For example, Ley *et al.* reported selective activation of phenylseleno glycoside **130** over thioglycoside acceptor **131** in application to convergent synthesis of GPI anchor of *Trypanosoma brucei* (Scheme 26).¹²⁶

This coupling was performed in the presence of MeOTf and resulted in the formation of trisaccharide **132** in 75% yield. The latter was then converted into glycosyl acceptor **133** which was glycosylated with selenoglycoside **134** in the presence of MeOTf. Recently, electrochemical activation of selenoglycoside donors over thioglycoside acceptor has been demonstrated.¹²⁸ The use of telluroglycosides as glycosyl donors was reported by Yoshida^{129,130} and Stick.^{131,132} These glycosyl donors can be activated either electrochemically^{129,130} or in the presence of MeOTf, NIS/*t*-BuOCl, or NBS/TMSOTf.¹³³ Selective activation of telluroglycosides over thioglycosyl¹³³ and selenoglycosyl acceptors¹³² has been demonstrated.

Orthoesters have been used as useful glycosyl donors for 1,2-*trans* glycosylation for decades.¹³⁴ Their activation is typically achieved in the presence of a Lewis acid or a mild electrophilic promoter, and these conditions typically permit their selective activation over a number of leaving groups of different classes. For example, it was demonstrated that ethylthio orthoester **136** can be activated over conventional thioglycoside **137** using NIS/TfOH (Scheme 27a).¹³⁵ Lopez *et al.* reported that *n*-pentenyl 1,2-orthoesters are activated over glycosyl fluoride acceptors in the presence NIS and Yb(OTf)₃.⁸⁸ Recently, Hotha *et al.* reported that *n*-pentenyl 1,2-orthoester **139** can be selectively activated over propargyl glycoside **85** in the presence of NIS/Yb(OTf)₃ (Scheme 27b).⁸⁹ Along similar lines, propargyl 1,2-orthoester **141** can be selectively activated over *n*-pentenyl acceptor **142** in the presence of AuBr₃ leading to trisaccharide **143** (Scheme 27c). Cyanoethylidene approach to 1,2-*trans*-glycosylation of tritylated acceptors has been extensively studied by Kochetkov and co-workers.^{136,137} As reported by Boons, this approach allows for selective activation of cyanoethylidene donor over *n*-pentenyl glycosyl acceptor in the presence of TrClO₄.^{120,138} Backinowsky *et al.* reported that 1,2-*O*-(1-cyanoethylidene) donors can be activated with TrClO₄ over thioglycoside acceptors.¹³⁹

Danishefsky and co-workers developed a convenient method for the preparation of 1,2-anhydro sugars from glycals using dimethyldioxirane (DMDO)¹⁴⁰ as an effective epoxidation reagent.¹⁴¹ This allowed to apply 1,2-epoxides as very effective glycosyl donors.^{142,143} For example, 1,2-anhydrosugar **145** generated from glycal **144** could be activated over glycal acceptor **146** in the presence of ZnCl₂ to afford 1,2-*trans*-linked disaccharide **147** in 81% (Scheme 28). The epoxidation-glycosylation sequence can be then reiterated to yield larger oligosaccharides, although similarly to other pre-activation type of couplings, this approach cannot be classified as the formal oligosaccharide synthesis via selective activations.

4. Multistep sequences based on selective activations

Studies presented in the previous sections allowed to compile a comprehensive database on reactivity of different classes of glycosyl donors, which led to the development of selective activation-based multistep oligosaccharide synthesis. Continuation of the activation sequence beyond previously discussed couplings of building blocks equipped with LG^a and LG^b requires the availability of a LG^c, which would withstand activation conditions for the LG^b, etc. However, these elongated multi-step sequences are not yet routinely available

(*vide infra*). This can be circumvented by performing additional modifications between glycosylations that allow repetition of the sequence involving repetitive LG^a and LG^b activations. An example of such approach is the synthesis of heparin-like pentasaccharide **157** by utilizing the diphenyl sulfoxide—triflic anhydride dehydrative protocol¹⁴⁴ for the activation of the hemiacetal **148** over thioglycoside acceptor **149** (Scheme 29).⁵⁷

The phenylthio moiety of the resulting disaccharide **150** was then directly coupled with glycosyl acceptor **151** using benzenesulfinyl piperidine (BSP)-triflic anhydride System developed by Crich.¹⁴⁵ The resulting trisaccharide **152** was then converted into the corresponding hemiacetal derivative **153**, which was selectively activated over thioglycoside acceptor **154** in the presence of diphenyl sulfoxide-triflic anhydride. The resulting tetrasaccharide **155** isolated in 51% yield was glycosidated with glycosyl acceptor **156** in the presence of the BSP/Tf₂O promoter system to furnish the target pentasaccharide **157** in 53% yield.

An example with the involvement of three leaving groups is depicted in Scheme 30, in which trichloroacetimidoyl is used as a LG^a, phenylselenyl as LG^b, and ethylthio as LG^c.³⁴ Thus, activation of trichloroacetimidate **158** over selenoglycoside acceptor **159** was achieved in the presence of TMSOTf. The resulting disaccharide **160** isolated in 90% was then coupled with thioglycoside acceptor **112** in the presence of AgOTf and K₂CO₃ leading to trisaccharide **161** in 81% yield. In principle, the thioethyl moiety of **161** can be activated further. A similar sequence using bromide (LG^a), selenoglycoside (LG^b) and thioglycoside (LG^c) was also reported.³⁴

Another relevant example is the use of the *S*-benzoxazolyl (SBox) moiety as LG^a, *S*-ethyl as LG^b, and *O*-pentenyl as LG^c depicted in Scheme 31.^{146,147} SBox glycosyl donor **114** was selectively activated over the SET acceptor **82** in the presence of AgOTf to produce disaccharide **162** in 99% yield. The latter disaccharide was glycosidated with the *n*-pentenyl acceptor **163** in the presence of MeOTf. Finally, the *n*-pentenyl moiety of the trisaccharide **164** was activated with NIS/TMSOTf. A similar example included the following three-step activation sequence performed in a one-pot fashion: SBox as LG^a, *S*-thiazolynyl (STaz) as LG^b, and *S*-ethyl as LG^c.¹⁴⁸

Very recently, the synthesis of a β-(1→6)-linked hexasaccharide via the five-step selective activation sequence employing six different leaving groups was developed (Scheme 32).¹⁴⁹ The synthesis began with the selective activation of thiocyanate donor **167** over STaz glycosyl acceptor **115** using Cu(OTf)₂. The STaz leaving group of disaccharide **116** was then directly activated over SBox acceptor **168** with benzyl bromide to give trisaccharide **169**. The SBox moiety of **169** was selectively activated over the fluoride acceptor **170** in the presence of MeOTf. The resulting tetrasaccharide **171** was glycosidated with thioglycoside acceptor **137** in presence of AgClO₄/Cp₂ZrCl₂ to provide pentasaccharide **172**. Finally, the *S*-ethyl leaving group of **172** was selectively activated over *n*-pentenyl acceptor **91** with MeOTf to furnish the hexasaccharide **173** in 72% yield.¹⁴⁹

5. Semi-orthogonal approach

The orthogonal approach makes use of two leaving groups, LG^a and LG^b, which can be independently activated one over another and *vice versa*. A semi-orthogonal strategy is based on a similar principle, but it requires the additional enforcement by electronic effects, similarly to that of the “armed-disarmed concept”. Overall, this concept combines advantages of both selective and chemoselective activation; its utility, however, is limited by the protecting groups that also often determine the stereoselectivity. It was demonstrated⁸⁷ that either armed or disarmed thioglycoside can be selectively activated over either armed or disarmed *n*-pentenyl glycosides in the presence of MeOTf. However, only armed *n*-pentenyl

could then be activated over a disarmed thioglycoside acceptor using IDCP as a mild promoter. Thus, *S*-ethyl donor **174** was selectively activated over *n*-pentenyl acceptor **142** in the presence of MeOTf (Scheme 33). The *n*-pentenyl moiety of the resulting trisaccharide **175** was then subjected to selective/chemoselective activation over *S*-ethyl acceptor **82** in the presence of IDCP leading to tetrasaccharide **176** in 92% yield.

This semi-orthogonal concept was recently extended to another suitable pair of leaving groups, namely fluoride and *n*-pentenyl.⁸⁸ While either armed or disarmed glycosyl fluorides underwent glycosylation with armed/disarmed *n*-pentenyl glycoside in presence of Yb(OTf)₃, only armed *n*-pentenyl glycosides could be activated over disarmed glycosyl fluorides in presence of IDCP. As depicted in Scheme 34, fluoride donor **177** was selectively activated over pentenyl **178** in the presence of Yb(OTf)₃. Conversely, the activation of armed *n*-pentenyl glycoside **180** was achieved selectively over fluoride **181** to afford disaccharide **182**. No activation of benzoylated *n*-pentenyl glycosides could be accomplished under these reaction conditions.

6. Orthogonal activation

The combination of two chemically distinct glycosylation reactions, in which one of the leaving groups is activated while the other one remains intact, and *vice versa*, has led to the discovery of the orthogonal strategy for oligosaccharide synthesis.¹² This unique, and virtually one of the most conceptually attractive techniques for expeditious oligosaccharide synthesis, requires the use of two orthogonal classes of leaving groups.^{150,151} As with the selective activation strategy, at the first step the glycosyl donor bearing LG^a is activated over the glycosyl acceptor bearing LG^b. Uniquely to the orthogonal strategy, however, the LG^b is then activated over LG^a of the glycosyl acceptor (Scheme 35). This activation sequence can then be reiterated to give straightforward access to larger oligosaccharides. Ideally, the orthogonal approach allows for an unlimited number of reiterations of the two orthogonal leaving groups, LG^a and LG^b, which is conceptually very attractive. On practice, however, the efficiency and yields of glycosidation are usually inversely correlated to the size of the glycosyl donor involved.^{12,152} And since this approach presumes the elongation of glycosyl donors, the yields are typically decreased dramatically at the later stage of the assembly.

6.1 Fluorides and thioglycosides

The classic variation of the orthogonal activation route introduced by Ogawa *et al.* involves building blocks bearing *S*-phenyl and fluoro leaving groups.¹² Phenyl thioglycoside **183** can be selectively activated over fluoride acceptor **184** in the presence of NIS/AgOTf (Scheme 36). The fluoro leaving group of disaccharide **185** can then be activated over thioglycoside acceptor **186** in the presence Cp₂Hf₂Cl₂/AgOTf. This selective activation sequence can be then reiterated; to illustrate this, trisaccharide *S*-phenyl donor **187** was activated over fluoride **184** to provide tetrasaccharide **188** in 66% yield.

6.2 Thioglycosides and thioimides

A combination of *S*-ethyl and *S*-thiazolynyl (STaz) leaving groups also represents a promising orthogonal pair. STaz glycosides can be activated selectively with AgOTf, whereas the ethyl thioglycoside can be activated with NIS and catalytic TfOH.¹¹⁰ This finding was applied to the synthesis of pentasaccharide **193**, as depicted in Scheme 37.¹⁵² Thioglycoside donor **189** was first activated over the STaz acceptor **115** in the presence of NIS/cat. TfOH. The resulting disaccharide **190** isolated in 98% yield was in turn activated over thioglycoside acceptor **137** with AgOTf to give trisaccharide **191** in 93% yield. The sequence was then reiterated as follows. Thioglycoside donor **191** was activated over STaz

acceptor **115** in the presence of NIS/cat. TFOH. The resulting tetrasaccharide **192** was selectively activated over thioglycoside acceptor **137** in the presence of AgOTf to give pentasaccharide **193** in 59% yield.

6.3 Thioimide-only (SBox and STaz glycosides)

A related approach involving orthogonal activation of STaz and SBox glycosides has also recently emerged.¹¹¹ SBox glycosides can be selectively activated with Cu(OTf)₂¹⁵² or Bi(OTf)₃¹¹³ over the STaz leaving group. As shown in Scheme 38, STaz leaving group that is typically more stable than SBox towards a majority of thiophilic activation conditions, can be also selectively activated over SBox in the presence of relatively mild alkylation reagents, benzyl bromide or methyl iodide. Mechanistic studies showed that the selective activation is based on the different activation modes of these leaving groups. Thus, it was found that preferential glycosidation of a certain thioimide is not simply determined by the strength of activating reagents; instead, the type of activation – direct (for SBox) vs. indirect (for STaz) – plays the key role. The activation of STaz donor **194** over SBox acceptor **168** in the presence of BnBr afforded disaccharide **195** in 76% yield. The latter could be then activated over STaz acceptor in the presence of Bi(OTf)₃ at 0 °C. The resulting trisaccharide **196** was isolated in 62% yield.

6.4 *n*-Pentenyl and propargyl activation

Recently, Hotha *et al.* reported a new promising pair of leaving groups: propargyl vs. *n*-pentenyl.⁸⁹ According to this study, NIS/TMSOTf served as an efficient activator for the selective activation of *n*-pentenyl glycoside **84** (see Scheme 18b). On the other hand, propargyl glycosyl donor **90** can be selectively activated over propargyl glycosyl acceptor **91** in the presence of AuBr₃ to afford disaccharide in 65% (see Scheme 19b). This activation is particularly efficient for benzoylated glycosyl acceptor **91** as glycosylation of its benzylated counterpart led to a modest yield of the respective disaccharide. This implies a more semi-orthogonal-like activation (*vide supra*) rather than purely orthogonal character of these two leaving groups.

7 Selective and orthogonal activations in modern high throughput technologies

7.1 Intramolecular glycosylations

The intramolecular aglycone delivery (IAD) approach was introduced by Hindsgaul¹⁵³ and Stork¹⁵⁴ as a reliable method to obtain β-mannosides. Ogawa *et al.* then reported the use of a *p*-methoxybenzyl (PMB) group at the C-2 position as a new stereocontrolling tether for β-mannosylation.^{38,155} The *p*-methoxybenzyl assisted IAD process was used as the key reaction for the construction of β-mannoside containing fragment that also involved selective activation (Scheme 39).^{39,117} Accordingly, thioglycoside donor **197** was linked to fluoride acceptor **184** via DDQ-mediated tethering. The resulting construct **198** was subjected to the treatment with MeOTf and DTBMP that allowed for selective activation of the *S*-methyl group over the fluoro group to afford β-mannoside **199**. The free hydroxyl group in **199** was then acetylated, and the resulting fluoride donor **200** was glycosidated with acceptor **201**. A similar approach was also investigated using polymer support.¹⁵⁶

7.2 One-pot synthesis

Conceptually, one-pot strategies offer the fastest pathway to oligosaccharides, as the sequential glycosylations are performed in a single flask (pot) and do not require purification of the intermediates. Of particular importance to the successful one-pot glycosylation is complete consumption of all building blocks and the high yield and complete

stereoselectivity in each glycosylation step. Many variations of the one-pot strategy have been developed and the reader should be referred to the recent review articles.^{157,158} Herein we focus our discussion on selective activation that requires a set of different leaving groups (LG^a, LG^b, LG^c) as illustrated in Scheme 40.

The first one-pot synthesis based on the leaving group based activation concept was reported by Takahashi and co-workers.³⁵ As depicted in Scheme 41, this synthesis involved the use of trichloroacetimidate donor **203**, which was selectively activated over thioglycoside **204** with TMSOTf. The SPh moiety of the intermediate tetrasaccharide was then directly glycosidated by adding glycosyl acceptor **205** and NIS/TfOH to provide hexasaccharide **206** in 50% yield over two steps. This approach incorporates advantages of the convergent block strategy according to which pre-synthesized oligosaccharide building blocks *i.e.* **203** and **205** are converged together during the final assembly. A number of related two-step one-pot syntheses have emerged, and the most representative examples are surveyed below. As depicted in Scheme 42a, reaction of bromide **207** and *S*-phenyl acceptor **208** was affected in the presence of silver triflate. The *S*-phenyl leaving group of the intermediate disaccharide was then glycosidated by adding glycosyl acceptor **209** and NIS. The resulting trisaccharide **210** was isolated in 84% yield over two steps.¹⁵⁹ In a similar fashion, tetrasaccharide glycosyl glycerol **214** which represents the core structure of a glycosylglycerolipid of *M. taiwanesis*, was synthesized as depicted in Scheme 42b.¹⁶⁰ A trisaccharide intermediate was formed from the glycosyl phosphite **211**, which was selectively activated over selenoglycoside acceptor **212** in the presence of TMSOTf. Subsequent addition of glycosyl acceptor **213** and NIS allowed to produce the target tetrasaccharide **214** in 46% yield overall. Seeberger and co-workers presented an efficient one-pot synthesis of a pentasaccharide **218** shown in Scheme 42c.¹⁶¹

A representative example involving three sequential glycosylation steps is shown in Scheme 43.¹⁴⁸ SBox donor **114** was activated over *S*-ethyl acceptor **82** with AgOTf. Thioethyl moiety of the intermediate was then activated over the added STaz acceptor **115** by the addition of NIS and catalytic TfOH. Finally, the STaz moiety was reacted with glycosyl acceptor **165** in the presence of additional quantity of AgOTf. As a result, linear tetrasaccharide **219** was obtained in 73% yield over three steps.

Utilizing longer sequences of selective activations are not yet routinely available. Although a number of one-pot syntheses of large oligosaccharides has emerged, all are based on mixed conventions, typically a combination of selective and chemo- or regioselective sequential activations. For example, Ley's group reported the synthesis of a GPI anchor involving building blocks with well defined levels of reactivity (Scheme 44).¹⁶² Thus, armed and disarmed glycosyl fluorides (**220**, **221**), armed and disarmed selenoglycosides (**222**, **223**) and thioglycoside **224** were all sequentially activated to provide the target linear pentamannoside **225** in 8% overall yield in four steps. Evidently, the first and the third steps involved chemoselective activations whereas the second and fourth steps involved selective activations of fluoride over SePh and SePh over SPh, respectively. Mukaiyama reported an elaborate one-pot sequence that resulted in the formation of a phytoalexin elicitor heptasaccharide **230** in 48% yield.¹⁶³ As depicted in Scheme 45, the synthesis of heptasaccharide **230** involved a combination of sequential selective (fluoride **226** over thioglycoside **227**) and chemoselective activations (armed SET disaccharide intermediate over disarmed acceptor **228**), as well as a convergent approach (4 + 3, building block **229**), all in one pot.

A similar target was obtained by Takahashi in a six-step one-pot synthesis of heptasaccharide using a Quest 210 manual synthesizer.¹⁶⁴ As depicted in Scheme 46, this synthesis required the sequential addition of seven reaction components **231–237** equipped

with four different leaving groups. Sequential activations employed herein include: activation of glycosyl bromide **231** (activated with AgOTf over *S*-ethyl acceptor), thioglycosides **232** and **233** (with MeOTf over fluoride acceptor **234**), tetrasaccharide fluoride (with Cp₂HfCl₂/AgOTf over *S*-phenyl acceptor **235**) and phenyl thioglycosides **236** and hexasaccharide (with DMTST in the armed-disarmed fashion). The resulting protected phytoalexin elicitor heptasaccharide **238** was isolated in 24% yield over six steps. To the best of our knowledge, this is the only selective activation-based synthesis that incorporates the elements of the orthogonal activations in one-pot (steps three and four).

7.3 Polymer-supported synthesis

Solid-phase synthesis has been developed and widely utilized in a routine preparation of oligopeptides and oligonucleotides, and is attracting renewed attention in connection with combinatorial chemistry.¹⁶⁵ The use of polymer supports in oligosaccharide synthesis has also been attractive and several intriguing approaches have been reported.^{166,167} Most of the known syntheses involve glycosyl acceptor-bound approach, but examples involving glycosyl donor bound strategies that allow for selective activations have also emerged. An example of a donor-bound approach utilizing selective activations on solid phase synthesis is the synthesis of the Le^b blood group antigen reported by Danishefsky and co-workers (Scheme 47).¹⁶⁸ Glycal connected to Merrifield's resin **239** was subjected to epoxidation with DMDO, followed by coupling with glycal acceptor **240** in the presence of ZnCl₂. Fucosyl fluoride donor **241** was then activated over polymer-bound glycal **242** in the presence of Sn(OTf)₂ and DTBP. These steps incorporate the elements of a two-directional concept developed by Boons.^{169,170} The resulting tetrasaccharide glycal **243** was then converted into the corresponding 2-amino thioglycoside **244** that was coupled with glycal acceptor **255**. The resulting pentasaccharide was then cleaved off of the polymer support to afford pentasaccharide **246** in 20% over-all. Selective activation of the SBox bound glycosyl donor over solution phase thioglycoside acceptor in the presence of TMSOTf was also reported.¹⁷¹

The application of the orthogonal strategy utilizing polymer support was described by Ogawa.¹³ To illustrate this concept, a recent representative example is depicted in Scheme 48.¹⁷² According to this approach, polymer-bound glycosyl donor **247** was activated selectively over fluoride acceptor **15** in the presence of DMTST. The resulting disaccharide **248** was activated over *S*-phenyl acceptor **249** in the presence of Cp₂Hf(OTf)₂. Finally, *S*-phenyl trisaccharide **250** was glycosidated with octanol in the presence of DMTST.

7.4 Ionic liquid supported synthesis

A promising technique for the tagged oligosaccharide synthesis that makes use of an ionic-liquid support has recently emerged.^{173,174} As with the polymer-supported^{166,167} and fluorous tag-supported^{175,176} syntheses, ionic liquid-supported assembly expedites oligosaccharide synthesis by eliminating the need for chromatographic purification of the intermediates. Herein, this approach is illustrated by an example that incorporates elements of orthogonal strategy making use of alternating activations of STol and F leaving groups and convergent approach (Scheme 49).^{177,178} (1-Methylimidazoliumhexafluorophospho)acetyl ionic liquid tag is readily introduced via the corresponding 6-chloroacetylated starting material by reaction with *N*-methylimidazole and potassium hexafluorophosphate.

Very recently, Gouhier and co-workers¹⁷⁹ reported efficient 1,2-*cis*-glycosylations using ionic liquid-supported thioglycoside building block **266** in a two-directional^{169,170} manner. First, thioglycoside **266** was employed as a glycosyl acceptor for the selective activation of trichloroacetimidate donor **265** in presence of TMSOTf (Scheme 50). The resulting α -

(1→4)-linked disaccharide **267** was then used as the glycosyl donor for the coupling with acceptor **268** that resulted in the formation of trisaccharide **269**.

8 Conclusions and future directions

It is critical to make complex carbohydrates more accessible to the general chemical, biochemical, and industrial audiences to keep pace with the exploding area of glycobiology. This can be only achieved by the development of methods and strategies for efficient oligosaccharide synthesis that would be applicable for both laboratory and industrial preparation. A number of excellent strategies that offer efficient routes to oligosaccharide assembly have already emerged. Important discoveries surveyed in this article have already allowed scientists to synthesize complex oligosaccharides and glycoconjugates for structural, biological, and medical studies. Nevertheless, carbohydrates of even moderate complexity still present a considerable challenge, even to experts. No expeditious strategy developed to date can offer an easy and reliable access to the full range of compounds of interest to glycoscientists. Some strategies offer a very efficient approach to a certain sequence, but in general each target still requires careful selection of methods, conditions, and strategies. Therefore, examples of conventional oligosaccharide synthesis using additional protecting/leaving group manipulations are still abundant.

The development of efficient and general methods for expeditious synthesis of complex carbohydrates will undoubtedly remain an important and active arena for scientific endeavors during the 21st century. In the coming years, glycoscientists are expected to have developed more simple, efficient, and flexible approaches to oligosaccharide assembly that will complement existing methodologies and bring our ability to obtain complex oligosaccharides to a significantly higher level. The recent innovations surveyed herein make contemporary glycoscientists well positioned to undertake further studies. Future developments may be expected to incorporate existing methodologies, and combinations thereof, while blending in new concepts and technologies.

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Scheme 1.
Traditional linear oligosaccharide synthesis.

Scheme 2.
Chemoselective activation strategy.

Scheme 3.
Selective activation strategy.

Scheme 4.
Selective activation of glycosyl bromide donor **1** over thioglycoside acceptor **2**.

Scheme 5.
Synthesis of tetrasaccharide **12** of *V. cholerae* O139.

Scheme 6.

Tri(1-pyrrolidino)phosphine oxide as the activator of glycosyl bromides in selective activations.

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Scheme 8.
Selective activation of glycosyl iodide **21** over glycosyl acetate **22** and thioglycoside **24**.

Scheme 9.
Selective activation of glycosyl fluorides.

Scheme 10. Selective activation of glycosyl fluoride **20** over thioglycoside.

Scheme 11.

Selective activation of hemiacetal donors over glycosyl acetate **35** (a) and thioglycoside **38** (b).

Scheme 12.

Selective activation of glycosyl acetate **40** (a), carbonate **43** (b), and *ortho*-alkynylbenzoate **46** (c) over thioglycoside acceptors.

Scheme 13.

Selective activation of trichloroacetimidates over thioglycoside **50** (a), *n*-pentenyl **53** (b) and propargyl glycoside **56** (c).

Scheme 14.

Selective activation of (*N*-phenyl)trifluoroacetimidate **58** over *n*-pentenyl glycoside **59** (a) and sequential activation of **61** and **62** (b).

Scheme 15.

Selective activation of 6-nitro-2-benzothiazole **65** over thioglycoside **66** and glycosyl fluoride **15**.

Scheme 16.

Selective activation of glycosyl phosphites over thioglycoside **70** (a) and phosphorodiamidate **73** (b).

Scheme 17.

Glycosyl phosphates in selective activation over O-pentenyl acceptor **76** (a) and thioglycoside **79** (b).

Scheme 18.

n-Pentenyl glycosyl donors in selective glycosylation over disarmed thioglycoside **82** (a) and propargyl glycoside **85** (b).

Scheme 19.

Application of 3-methoxy-2-pyridyl donor **87** (a), and propargyl glycoside **90** (b) in selective activations.

Scheme 20.

Utilizing glycosyl sulfoxides **93** and **97** in selective activation as a part of the synthesis of the Le^a antigen.

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Selective glycosidation of thiocyanate **99** (a) and 1-piperidinecarbodithioate **102** (b) over thioglycoside acceptors.

Scheme 22.

SBox glycosides in selective activation over O-pentenyl acceptor **106** (a) and thioglycoside acceptor **109** (b).

Scheme 23.

STaz glycosides as glycosyl donors (a) and glycosyl acceptors (b) in selective activations.

Scheme 24.

Selective activation of thioglycosides over glycosyl fluoride **118** (a), S-thiazolynyl **115** (b), and *n*-pentenyl **122** (c) acceptors.

Scheme 25.

Selective activation of thioglycosides **124** and **128** over O-propargyl glycosyl acceptors.

Scheme 26.

Convergent synthesis of pentasaccharide **135** using selective activation of selenoglycosides over thioglycosides.

Scheme 27.

Selective activation of orthoesters over thioglycoside **137** (a), propargyl glycoside **85** (b), and pentenyl glycoside **142** (c).

Scheme 28.

Glycal-epoxide method for oligosaccharide synthesis.

Scheme 29. Selective activation-based synthesis of heparin analog **157**.

Scheme 30.

Selective activation utilizing three different leaving groups.

Scheme 31.

Three-step SBox → SEt → *n*-pent sequential selective activation for the synthesis of tetrasaccharide **166**.

Scheme 32.

Selective activation utilizing six different leaving groups in the synthesis of 1,2-*trans* hexasaccharide **173**.

Scheme 33.

Semi-orthogonality of thioglycosides and *n*-pentenyl glycosides applied to the synthesis of tetrasaccharide **176**.

Scheme 34. Semi-orthogonality of *n*-pentenyl glycosides and glycosyl fluorides.

Scheme 35.
Orthogonal strategy for oligosaccharide synthesis.

Scheme 36.
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Scheme 37.
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Scheme 38.
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Scheme 40.

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Typical examples of two-step one-pot oligosaccharide syntheses of oligosaccharides **210**, **214** and **218**.

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Mukaiyama's one-pot synthesis involving the elements of selective, chemoselective and convergent concepts.

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Scheme 48.

Orthogonal glycosylation reactions on solid phase for synthesis of trisaccharide **252**.

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Scheme 49.

Orthogonal activation of fluoride over thioglycoside and *vice versa* on ionic liquid support

Scheme 50.

Selective activation of trichloroacetimidate over thioglycoside on ionic liquid support.