One-Pot Glycosylation (OPG) for the Chemical Synthesis of Oligosaccharides

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Abstract: This review provides a comprehensive survey of the "one pot glycosylation" (OPG) strategy for the chemical synthesis of oligosaccharides, covering literatures from the first example reported by Kahne and Raghavan in 1993 through May 2003. The essence of the OPG is to distinguish the reactivity difference of a pair of the glycosylation donors or acceptors so as to carry out two glycosylation steps sequentially without purification of the first-step coupling product. Accordingly, the literature reports are grouped based on the major stereoelectronic factors causing the reactivity differences, those include the "armed-disarmed effect", "orthogonality of leaving groups", "distinguishable acceptors", and "the hybrid". "The hybrid" OPG procedure takes advantage of a combination of the reactivity disparity of a set of the armed-disarmed donors, orthogonal leaving groups, as well as acceptors so as to proceed three or more steps of glycosylation sequentially in one pot. Relevant conception and exploitation of the reactivity differences of the donors and acceptors in the synthesis of oligosaccharides, which finally evolve the OPG or advance parallelly, are briefly described at the beginning.

1. INTRODUCTION

The need for oligosaccharides and glycoconjugates of defined composition to serve as molecular tools for biological and medicinal studies have driven impetuously the field of oligosaccharide synthesis especially since 1980s. The flourishing alternatives thus developed for glycosylation and protection, sometimes seemingly overgrown, have in facts laid a ground for the assembly of oligosaccharides in unprecedented efficient fashions [1-8]. Among the most promising ones is the "one-pot glycosylation" (OPG) strategy. An OPG carries out two or more glycosylation steps sequentially without the requirement of protecting group manipulation and intermediate isolation in between, thus removes the major burden in the conventional chemical synthesis of oligosaccharides in contrast to the natural enzymatic way. To realize the OPG, the reactivity difference of the donors/acceptors involved must be well distinguished by a set of glycosylation conditions, and these conditions sequentially performed in one pot need to be compatible. Such a high demanding was first fulfilled by Kahne and Raghavan, seems occasionally, in 1993 [9]. Through May 2003, nearly 50 fine designed OPGs have been published, those from the group of Wong have been accounted [10]. And we present here a comprehensive treatment of this topic.

According to the major factors creating the reactivity disparity of glycosylation donors/acceptors, the OPGs are divided into four groups in the present review, namely, "OPG steered by armed-disarmed donors", "OPG steered by orthogonal leaving groups", "OPG steered by distinguishable acceptors", and "the hybrid OPG". Within each group, a chronological order is largely followed. Before going to these topics, relevant conception and exploitation of the reactivity differences of the donors and acceptors in the synthesis of oligosaccharides, which finally evolve the OPG strategy or develop parallelly, are briefly described.

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2. RELEVANT CONCEPTS AND PROCEDURES

2.1 Historical Perception on the Reactivity of Glycosylation Donors/Acceptors

In the seminal review of 1982, Paulsen concluded the observations during oligosaccharide synthesis as such: "The reactivities at the anomeric center of the glycosyl component and of the OH group of the reaction partner depend very strongly on the type of blocking pattern of the two compounds. A variation of the blocking pattern can exert a decisive influence on the coupling step. Conformation and steric influences, and the molecular sizes of the two partners are also significant" [1].

2.2 "Armed-Disarmed" Concept

The previous view on the reactivity difference of glycosyl donors resulting from the blocking pattern was enlarged by Fraser-Reid and coworkers, in 1988, to such a level that it could be thoroughly distinguished and put into a chemoselective glycosylation. [11]. Thus, *n*-pentenyl glycoside **1**, "armed" with the electron-donating benzyl groups, was selectively activated with IDCP (iodonium dicollidine perchlorate) to couple with *n*-pentenyl glycoside **2**, which is "disarmed" with the electron-withdrawing acetyl groups, providing disaccharide **3** in 62% yield without detection of the self coupling products of **2** (Scheme **1**). The resulting "disarmed" **3** is obviously a donor capable of further glycosylation under stronger conditions.

Fraser-Reid *et al.* rationalized the armed-disarmed effect as such: "Reaction of a glycosyl donor with an appropriate electrophile gives a positively charged intermediate which is less favorable when there is an adjacent electron-withdrawing group (for example OCOR, as in a disarmed

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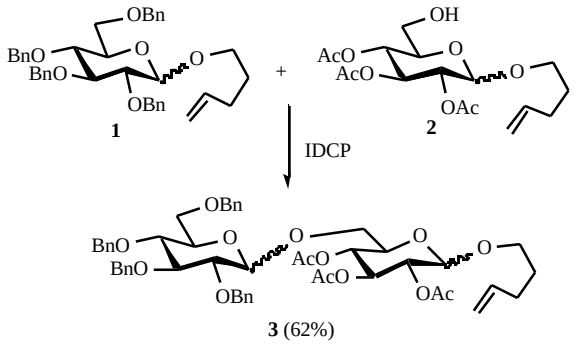
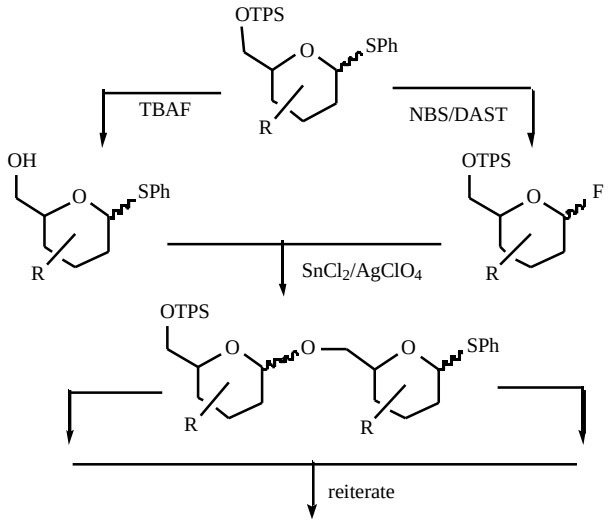


Scheme 1. A prototypical "armed-disarmed" glycosylation.

donor) than when there is an adjacent alkoxy group (as in the armed counterpart). The latter therefore reacts faster and if, in the reaction medium, there is a disarmed species carrying a free hydroxyl group, a pathway based on Le Chatelier's principle can be envisaged that leads to products of cross-coupling with (virtually) none of the self-coupled analogue" [12]. Based on these mechanistic rationales, the armed-disarmed concept, first recognized in *n*-pentenyl glycosides, was rapidly extended to other types of glycosyl donors, such as thioglycosides [13] and glycals [14]. And the torsional effect caused by cyclic acetal protections was also realized [15].

2.3 "Two-Stage Activation" and "Orthogonal Glycosylation" Strategies

After successful practice with thioglycosides and glycosyl fluorides, Nicolaou and coworkers have developed, since 1984, the "two-stage activation" strategy for the efficient synthesis of oligosaccharides. [7, 16]. This reiterative procedure utilizes the differential and orthogonal reactivities of glycosyl fluorides, phenylthioglycosides, and silyl ethers to achieve a sequential growth of the oligosaccharide chain (Scheme **2**).



Scheme 2. "Two-stage activation". procedure for the reiterative oligosaccharide synthesis.

The "orthogonal glycosylation" strategy described by Kanie, Ito, and Ogawa, in 1994, activated the glycosyl fluorides (Cp_2HfCl_2, $AgClO_4$, -78 ^oC - rt) and thioglycosides (NIS, AgOTf, -50 ^oC - rt) for glycosylation in an orthogonal fashion, so that the requirement in the "two-stage activation" for conversion of thioglycosides into fluorides for the next step glycosylation was joyfully removed [17].

In complementary to the "orthogonal" effect, leaving groups of a similar type but with different steric or electronic nature were also found possible for chemoselective glycosylations, such as glycosylations between phenyl-selenoglycosides and thioglycoside [18] and between thioglycosides with different substituents on the anomeric sulfur, termed "active-latent" donors [19]. In a broad sense, "orthogonal effect" covers any distinguishable effects caused by the leaving groups of the glycosyl donors on the glycosylation selectivity.

2.4 "Two-Directional Glycosylation" Strategy

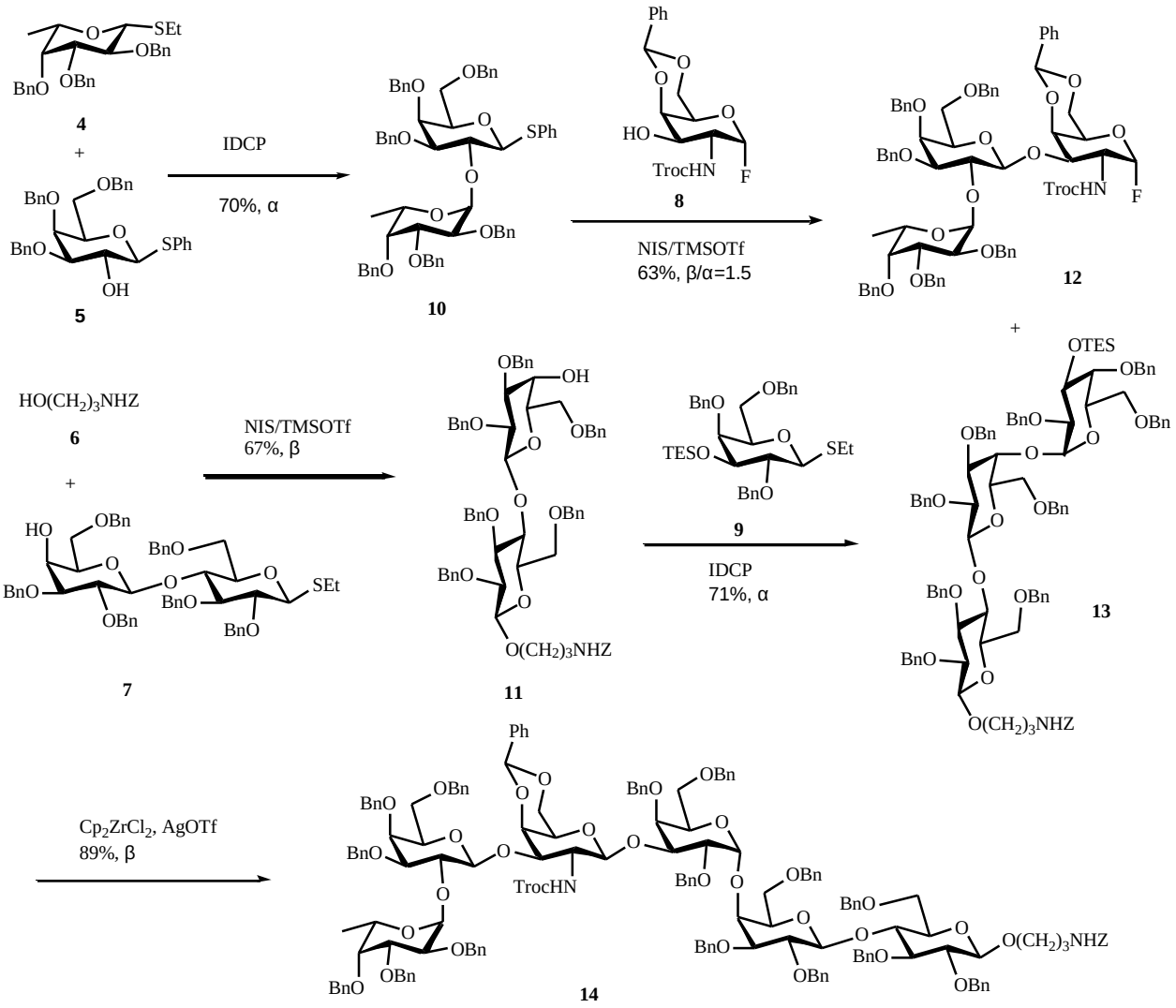
The reactivity difference between hydroxyl groups of the acceptors, caused by steroelectronic effects, has enabled the regioselective glycosylation to be a quite common practice [20]. Furthermore, several protected forms, such as trityl [21] and silyl ethers [22], which are normally inert toward glycosylation, have been found to be capable of direct glycosidation under some conditions. Thus an additional level for reactivity manipulation in the oligosaccharide synthesis is provided. Utilizing the reactivity disparity of both the donors and acceptors, Boons and Zhu developed a "two directional glycosylation" strategy [22-24]. A remarkable example is shown in Scheme **3** [24]. The protected hexasaccharide derivative of the tumor-associated antigen Globo-H (**14**) was assembled from six well-designed building blocks (**4**-**9**) *via* five successive steps of glycosylation. Not a single step for protecting group transformation was needed. Whereupon, the reactivity disparity between the coupling pair of donors (ethyl thioglycoside **4**/phenyl thioglycoside **5**, thioglycoside **10**/fluoride **8**) and acceptors (primary alcohol **6**/secondary alcohol **7**, alcohol **11**/TES ether **9**) were fully distinguished.

3. OPG For the Chemical Synthesis of Oligosaccharides

The above mentioned "armed-disarmed", "two-stage activation", "orthogonal glycosylation", as well as the hybrid "two-directional glycosylation" strategies are, in essence, a matter of reactivity tuning, so as to perform two or more steps of glycosylation successively without the need of protecting group manipulation in between. OPG strategy advances one step further where a set of compatible conditions are used for the sequential glycosylation so that the purification of the coupling intermediates is no long required.

3.1 OPG Steered by Armed-Disarmed Donors

Application of the armed-disarmed concept for an OPG was first established by Ley and coworkers in 1994 (Scheme **4**) [25]. Coupling of the armed thioglycoside **15** with disarmed **16** (NIS/TfOH) provided disaccharide **17** as the sole coupling product (as monitored by TLC), without detection of the self-coupling products of **16**. Upon addition of **18** and an additional portion of the promoters, the nascent



Scheme 3. A "two-directional glycosylation" strategy toward the synthesis of a hexasaccharide derivative of the tumor-associated antigen Globo-H.

disarmed **17** was activated and coupled with **18** to give trisaccharide **19** in a satisfactory 62% yield, equal to a *per* glycosylation yield of 79%.

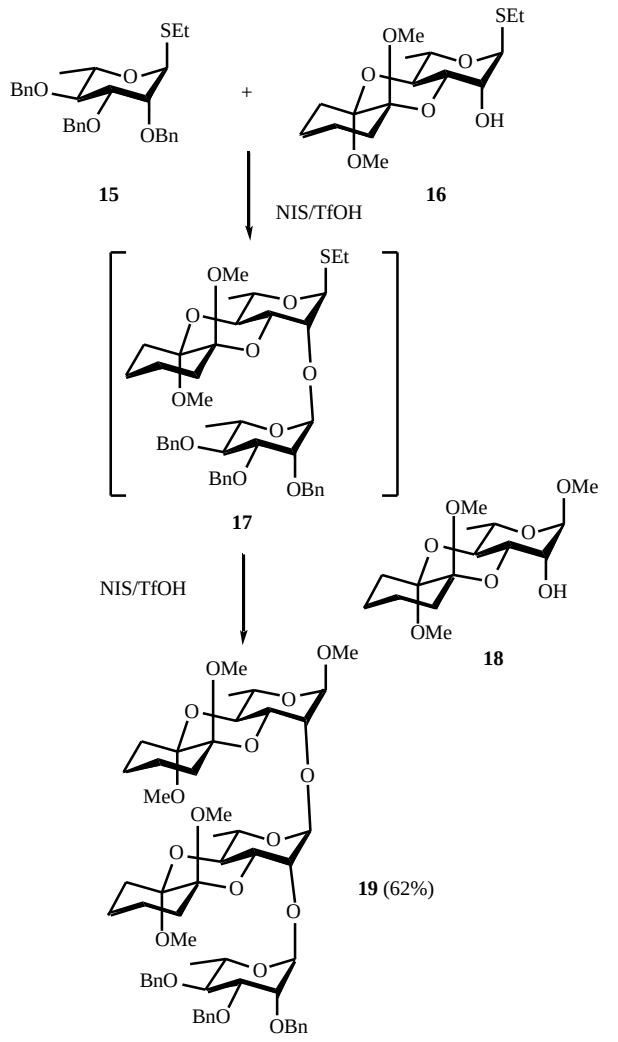
In 1997, the OPG of armed-disarmed thioglycosides was successfully employed in our total synthesis of the complex resin glycoside, tricolorin A (Scheme **5**) [26]. The armed thioglycoside **21** was selectively activated at –15 °C (NIS/TfOH) to glycosylate the disarmed **20**, the resulting **22** was then activated in the presence of an additional portion of NIS/TfOH at room temperature to couple with the newly added acceptor **23**, affording **24** in 43% isolated yield.

Similar protocol was also applied by Kondo *et al.*, in 1998, in the synthesis of Le^x oligosaccharide derivatives (**28**) (Scheme **6**) [27].

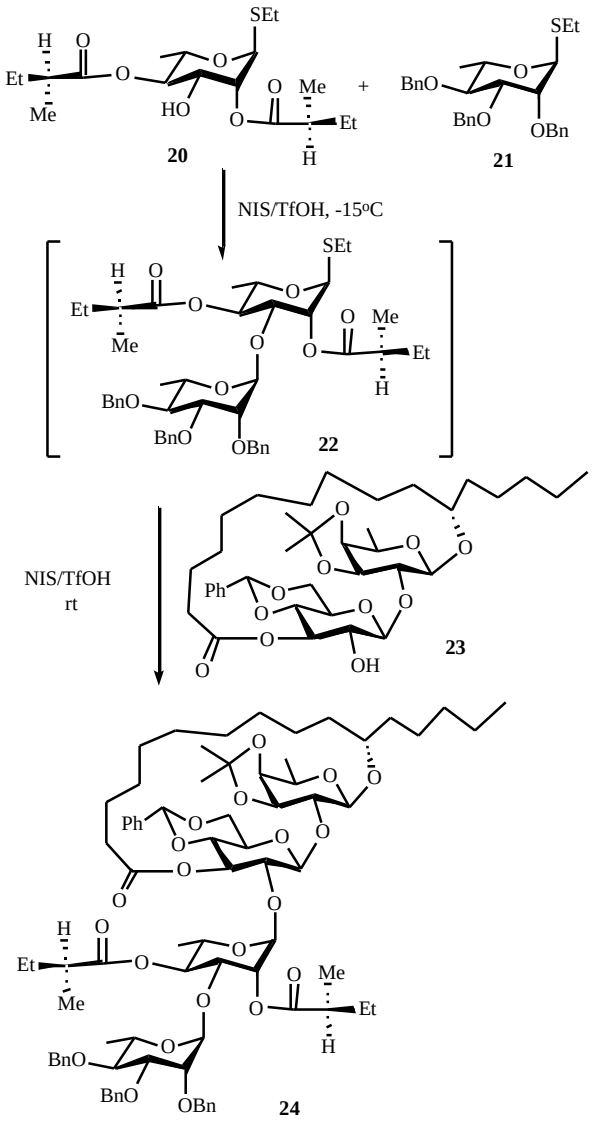
In 1999, Wong and coworkers contributed a general procedure for the quantitative measurement of the relative reactivities of the *p*-methylphenyl thioglycoside (STol) donors which are either fully protected or have one hydroxyl group exposed [28]. Thus, the structural effects of different monosaccharide cores and different protecting groups on the reactivity of each thioglycoside donors, which are previously obscure or simply classified as armed-disarmed, were accurately characterized and quantified. Furthermore, they compiled the relative reactivity values (RRVs) into a computer program, Optimer™, which can suggest optimal combinations of glycosyl building blocks for an OPG synthesis of the target oligosacchrides.

A concept-prove assembly of 33 linear or branched oligosaccharides based on RRVs was then provided. [29]. A representative synthesis is shown in Scheme **7**. The thioglycoside donor **29** (RRV = 7.2 x 10^4), thioglycoside donor/acceptor **30** (RRV = 142.9), and acceptor **32** (RRV = 0) were confidently chosen for the OPG synthesis of trisaccharide **33**.

Wong and coworkers have been expending the RRV database while achieving programmable OPG synthesis of biologically significant oligosaccharides [10]. An OPG strategy for a rapid assembly of the Globo H hexasaccharide



Scheme 4. OPG synthesis using armed-disarmed thioglycosides (**15** *vs.* **16**).



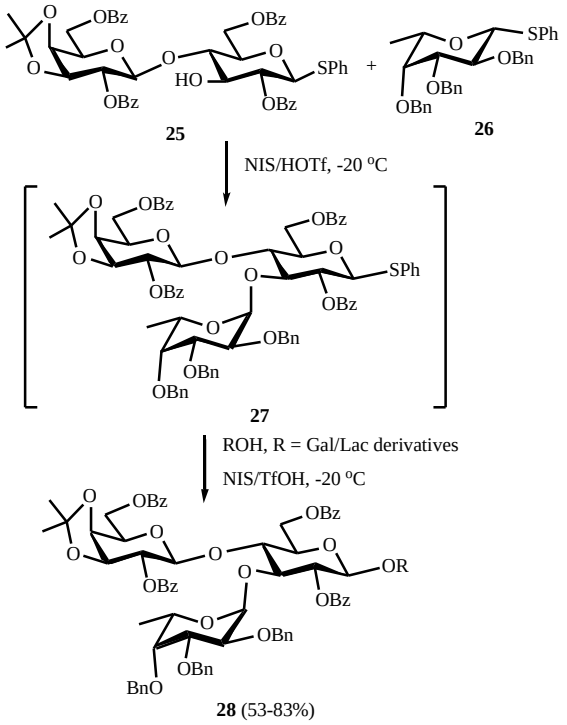
Scheme 5. OPG synthesis toward the resin glycoside tricolorin A using armed-disarmed thioglycosides (**21** *vs.* **20**).

is shown in Scheme **8** [30]. The flow of the OPG synthesis toward hexasaccharide **41** by thio-monosaccharides **34**-**36** and **39** and acceptor **40** was only interrupted at **37**, where a selective deprotection of the Lev group (**37** → **38**) was required for the following glycosylation.

Disaccharides and oligosaccharides could be viewed as monosaccharides with sugar substitutents, therefore, have their own RRVs and can be used as components in the OPG. In a synthetic route toward Lewis Y oligosaccharide hapten, a colon-rectal cancer antigen determinant, Wong *et al.*, realized a OPG synthesis of the hexasaccharide **45** employing monosaccharide donor **42**, disaccharide donor/acceptor **43**, and disaccharide acceptor **44** (Scheme **9**). [31]. The RRV of **42** is only six times larger than the RRV of **43**, nevertheless, a selective activation of **42** was achieved at –70 °C to bis-glycosylate **43**, the thio-function of which was kept latent until the next glycosylation with **44**.

Recently, Wong and coworkers added thioglycoside building blocks for the sialylated oligosaccharides [32] and the *N*-acetyllactosamine oligomers [33] to the Optimer database. Shown in Scheme **10** is an OPG synthesis of the acetyllactosamine trimer (**49**).

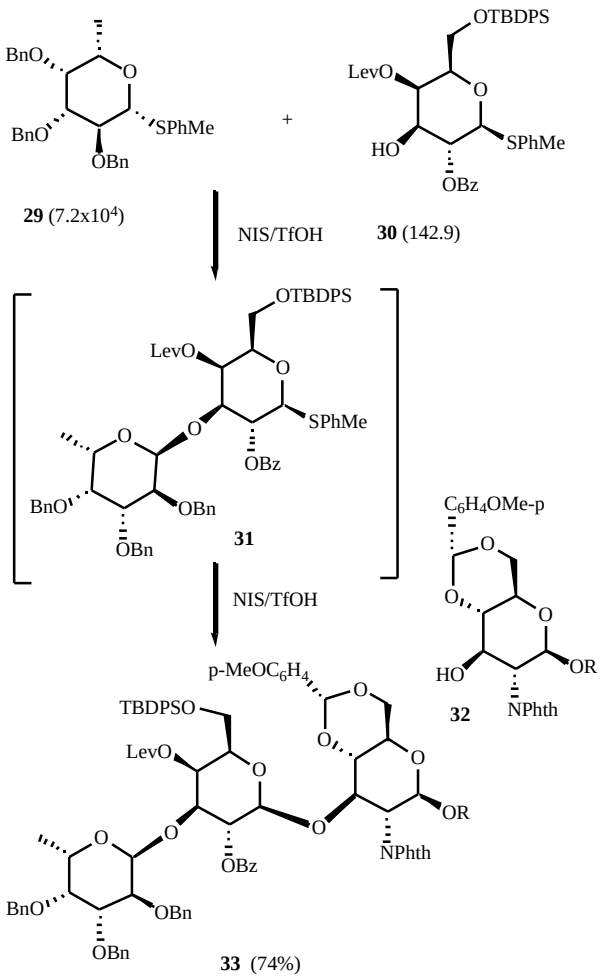
Adding stronger or more equivalents of the promoters or raising the reaction temperature after the completion of the first glycosylation is the usual way to force the second glycosylation to take place in the reactivity-based OPG. Oscarson and coworkers demonstrated that changing a reaction medium could also have the OPG done (Scheme **11**) [34]. Thus, the reactivity-based selective coupling of the thioglycosides **50** and **51** was achieved in Et_2O (NIS/AgOTf), but not in CH_2Cl_2, where a complex mixture was produced due to the activation of both components. Adding acceptor **52** and additional promoters in CH_2Cl_2, but not in Et_2O, realized the second glycosylation, affording **53** in high yield. Such a technique was later successfully used in the OPG syntheses of the glucosamine oligosaccharides by Baasov *et al*. (Scheme **12**) [35]. In combination with the armed-disarmed glycosylation with Troc and Phth protected



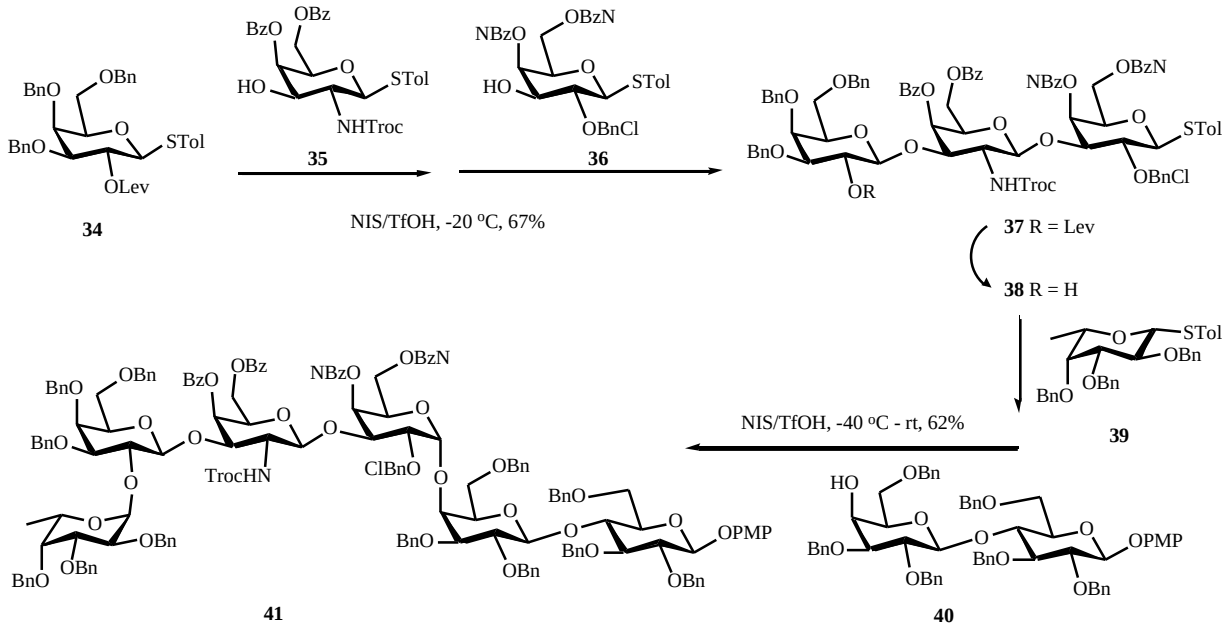
Scheme 6. OPG synthesis toward Le^x oligosaccharides using armed-disarmed thioglycosides (**26** *vs.* **25**).

thioglycosides, they were able to realize a three-step OPG synthesis of the glucosamine tetrasaccharide **58**.

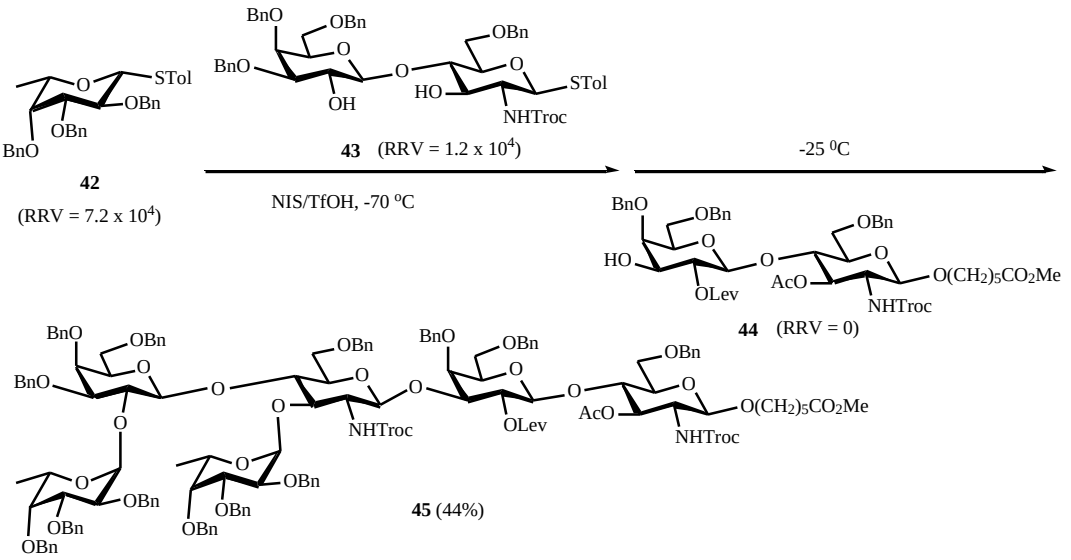
A new promoter system for the OPG of armed-disarmed thioglycosides was reported by Mukaiyama *et al.* in 2000 (Scheme **13**) [36]. The selective activation of the armed thioglycoside **59** was achieved by $TrB(C_6F_5)_4$/PhthNSEt. Subsequent addition of NIS and acceptor **61** forced the second glycosylation to afford the trisaccharide **62**.



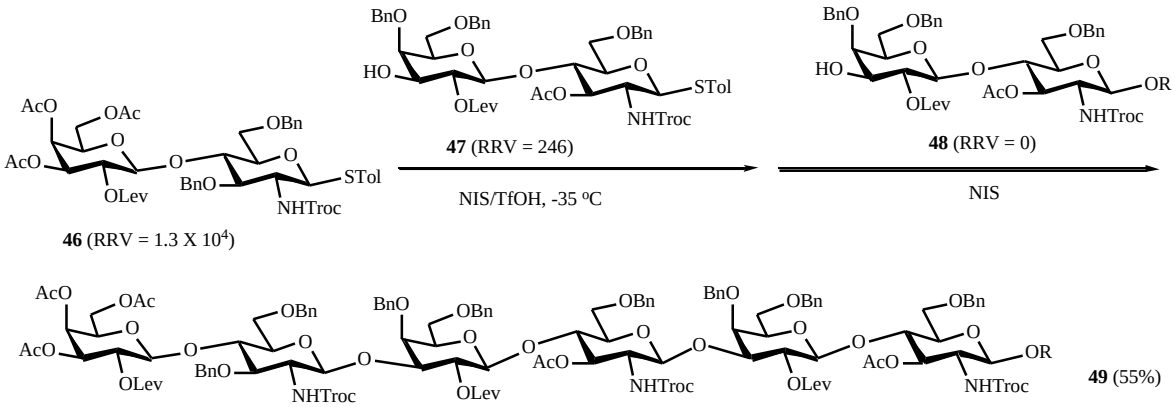
Scheme 7. A representative RRVs-based OPG synthesis using thioglycosides (**29** *vs.* **30**).



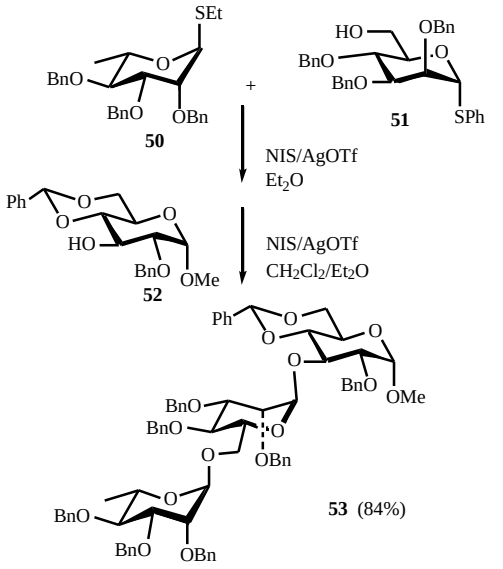
Scheme 8. Programmable reactivity-based OPG toward the Globo H hexasaccharide using thioglycosides.



Scheme 9. Programmable reactivity-based OPG synthesis toward the Le^y hapten using thioglycosides.



Scheme 10. Reactivity-based OPG synthesis of *N*-acetyllactosamine oligomers using thioglycosides.



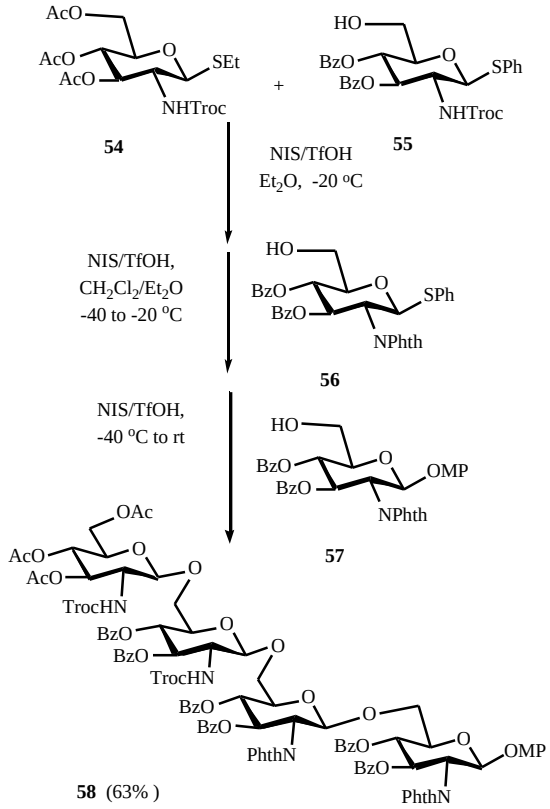
Scheme 11. Reactivity-based OPG synthesis controlled by varying solvents.

Although the armed-disarmed steered, or more broadly "reactivity-based" OPG has been largely relied on thioglycosides. In 1998, Ley and co-workers have noticed the capability of armed-disarmed glycosyl fluorides for OPG synthesis of oligosaccharides (Scheme **14**) [37].

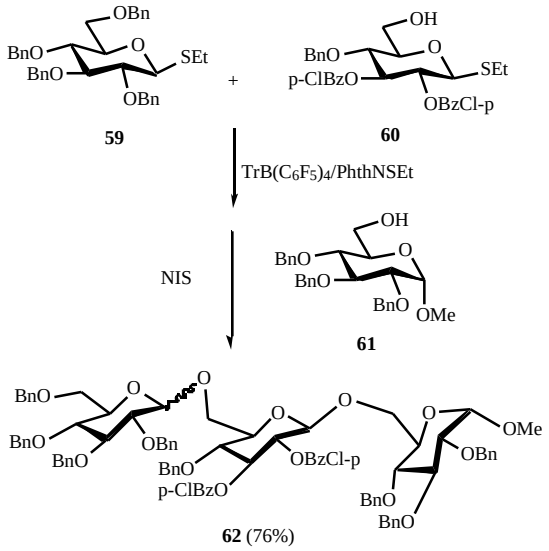
Recently, Mukaiyama and Chiba developed armed-disarmed glycosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidates (glycosyl thioformimidates) for OPG synthesis (Scheme **15**) [38]. The first step coupling between armed **67** and disarmed **68** was performed in the presence of a catalytic amount of TfOH at –78 °C, and the subsequent second glycosylation took place upon addition of the acceptor **69** and raising the temperature gradually to 0 °C.

3.2 OPG steered by the Orthogonal Leaving Groups

In 1994, Takahashi and coworkers firstly transformed the "orthogonal glycosylation" procedure into an OPG fashion (Scheme **16**) [39]. Thus, glycosyl bromide **71**, imidate **72**, or fluoride **73** was activated in the presence of AgOTf or BF_3OEt_2 to couple with thioglycoside acceptor **74**, the resulting thio-disaccharide was then activated under the action of the existing AgOTf or BF_3OEt_2 in combination



Scheme 12. Reactivity-based OPG synthesis of glucosamine oligosaccharides.

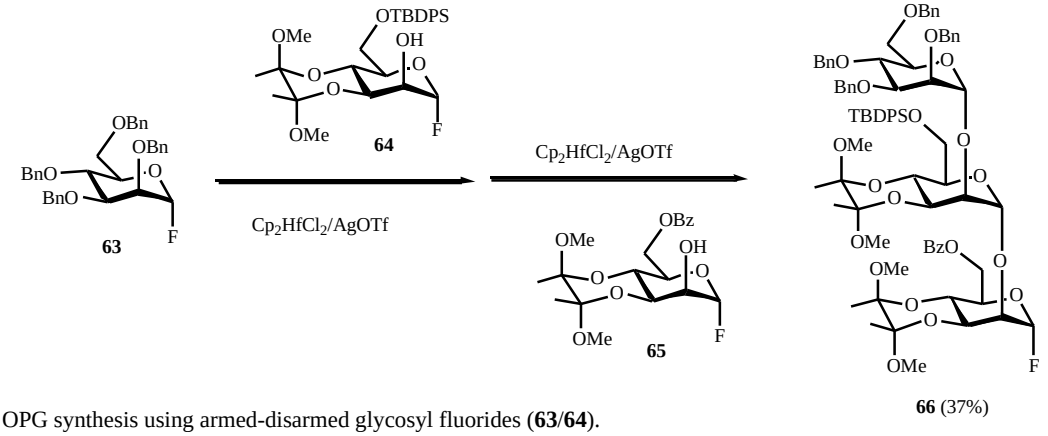


Scheme 13. OPG using armed-disarmed thioglycosides with $TrB(C_6F_5)_4$/PhthNSEt/NIS as the promoter system.

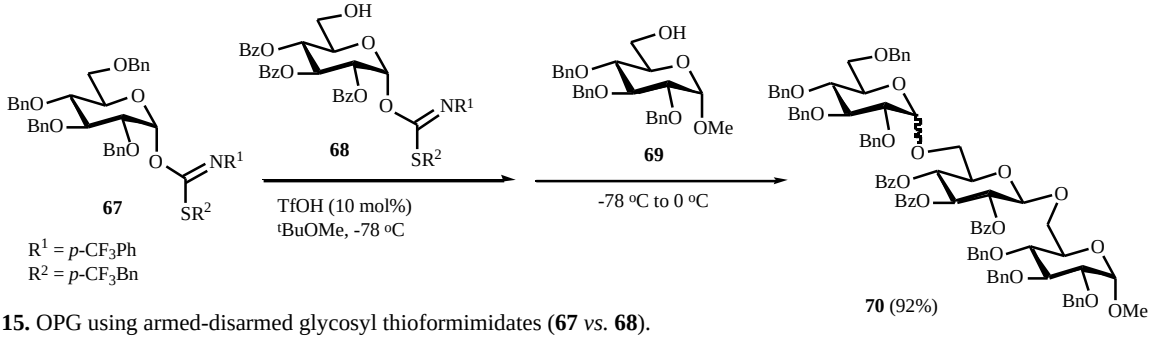
with an additional portion of NIS to couple with the newly added acceptor **75**, leading to the corresponding trisaccharide (**76**, **77**). Shortly, Takahashi *et al*. applied this OPG protocol to a successful assembly of the phytoalexin hexaglucan (Scheme **17**) [40].

At the same year, Chenault and Castro reported an OPG protocol with orthogonal isopropenyl glycoside (**82**) and *n*-pentenyl glycoside (**83**). However, the overall yields were not satisfactory (Scheme **18**) [41].

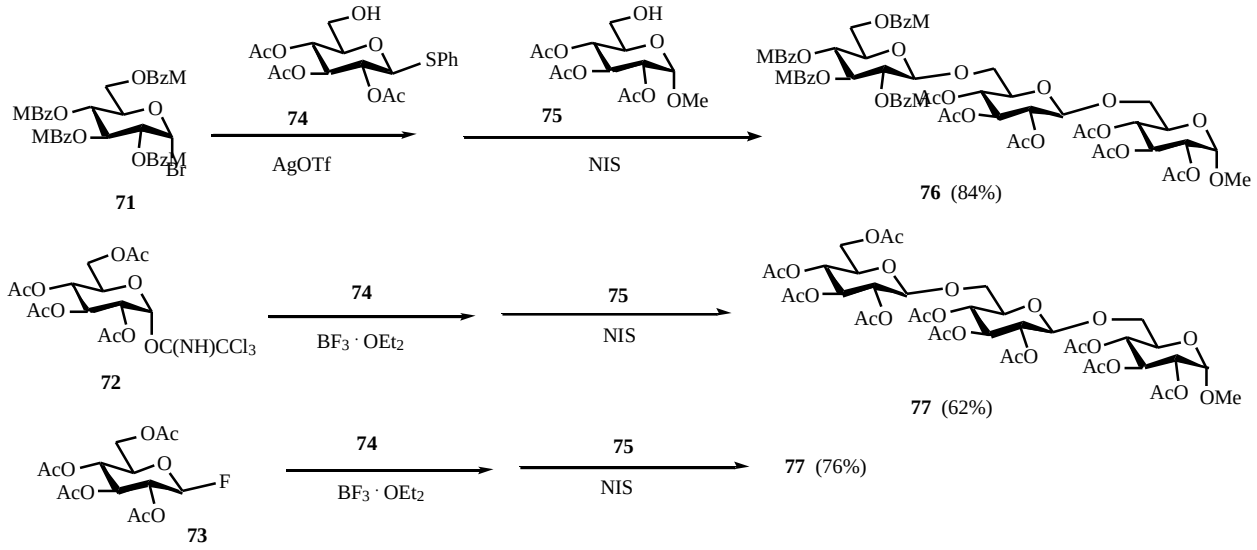
Ley and coworkers paired selenoglycosides and thioglycosides for OPG, while the orthogonality of these



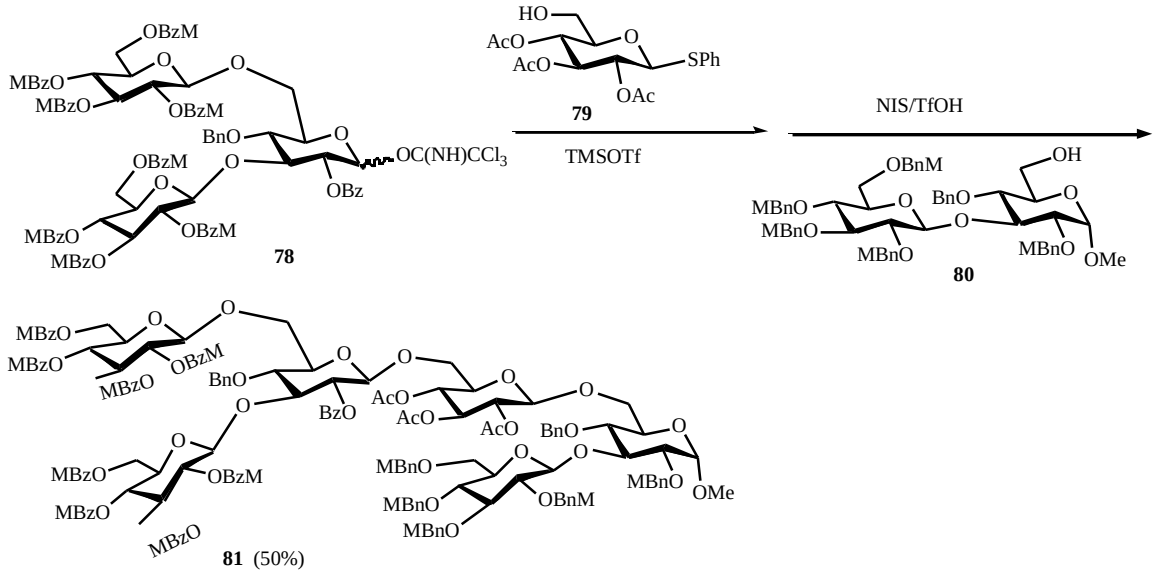
Scheme 14. OPG synthesis using armed-disarmed glycosyl fluorides (**63**/**64**).



Scheme 15. OPG using armed-disarmed glycosyl thioformimidates (**67** *vs.* **68**).



Scheme 16. Prototypical representatives of OPG using orthogonal leaving groups (glycosyl bromide **71**, imidate **72**, or fluoride **73** *vs.* thioglycoside **74**).

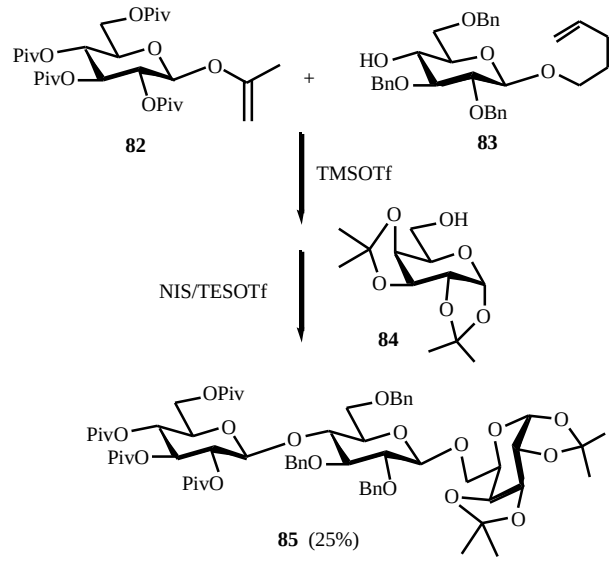


Scheme 17. OPG synthesis of phytoalexin hexaglucan using orthogonal imidate (**78**) *vs.* thioglycoside (**79**).

pairs might require additional enforcement by the structural effects (e. g., the armed-disarmed effect) (Scheme **19**) [42].

The OPG with orthogonal glycosyl imidates and thioglycosides might be more attractive for a practical synthesis due to the popularity of these two types of donors. Thus, we were able to prepare a group of natural diosgenyl saponins in a highly efficient parallel manner. [43, 44]. A representative is shown in Scheme **20**. The first step coupling between imidate donor **90** and thioglycoside acceptor **91** required only 0.1 equivalent of TMSOTf at –70 ^{o}C, while addition of 1.0 equivalent of NIS and the acceptor **92** promoted the second glycosylation.

Glycosyl phenylcarbonates have also been paired with thioglycosides by Mukaiyama *et al* to achieve the OPG synthesis of oligosaccharides (Scheme **21**) [45, 46]. However, the overall yields (62%-85%) were lower compared to those obtained by OPG using glycosyl imidates in the first step. In addition, only 1→6 linkages were made by this protocol. Mukaiyama and coworkers then also modified the OPG with glycosyl fluorides and thioglycosides. The first step glycosylation with the fluoride donors was promoted by 20 mol% TfOH in the coexistence of 5 Å MS in Et_2O, generating the corresponding α anomers predominantly in the absence of a neighboring control (Scheme **22**) [47]. These two OPG protocols were proved

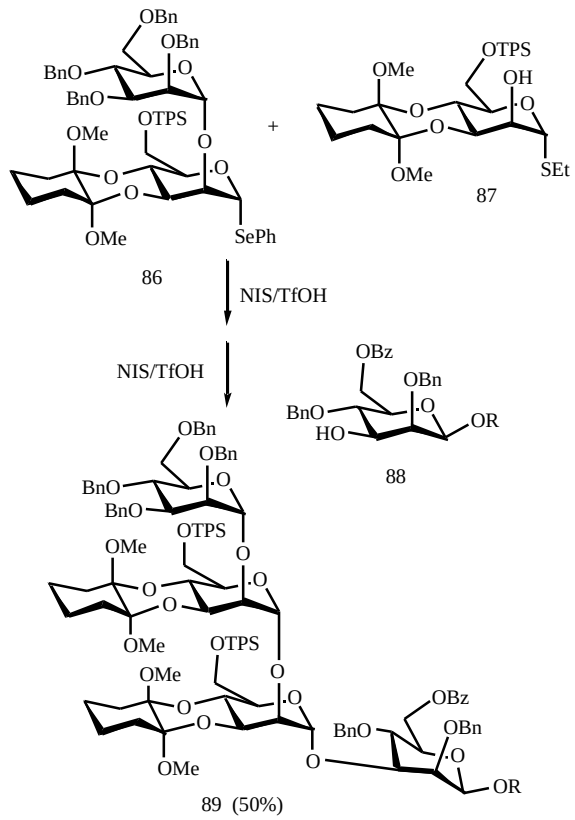


Scheme 18. OPG with orthogonal isopropenyl (**82**) *vs. n*-pentenyl glycoside (**83**).

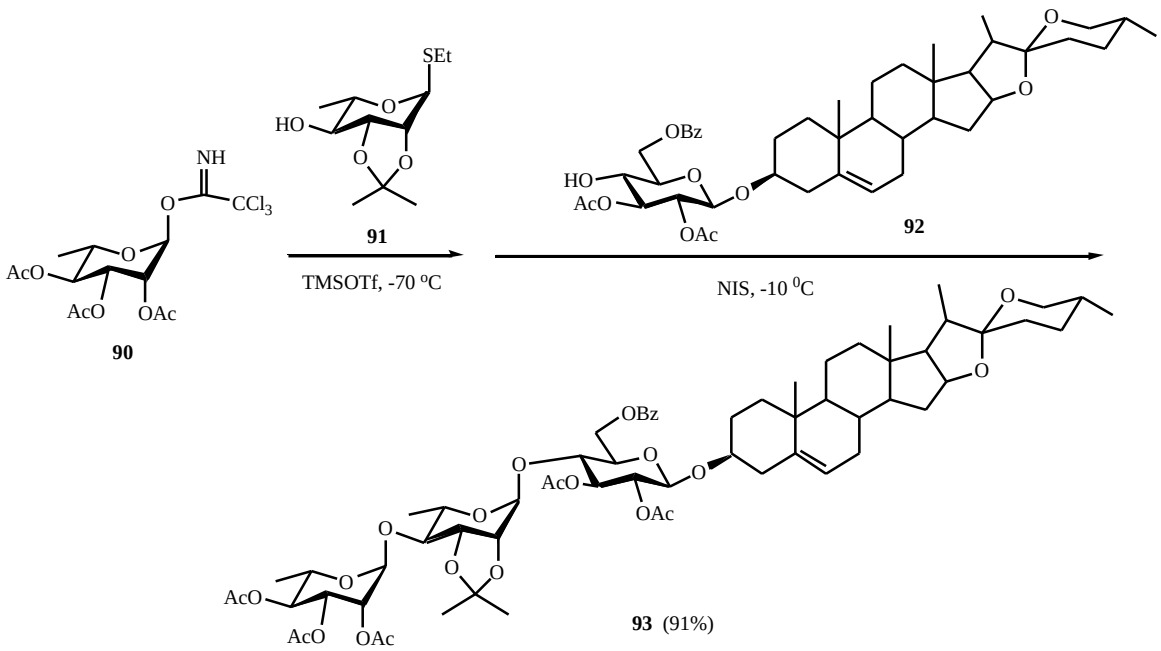
successful in the synthesis of the F1 α antigen (Scheme **23**) [48].

3.3 OPG Steered by Distinguishable Acceptors

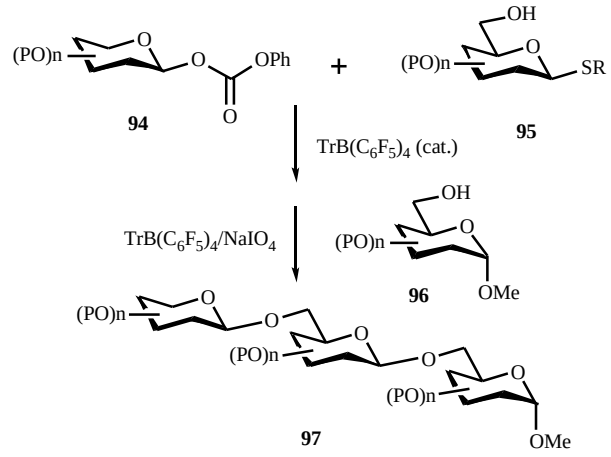
In 1997, Boons and Zhu published an excellent OPG protocol basing on the reactivity disparity between hydroxyl groups of a glycosyl donor (**109**) and an acceptor (**110**) (Scheme **24**) [49]. In the right flask, the "disarmed" primary OH of the thioglycoside donor **109** is less active than the "armed" primary OH of the acceptor **110**, therefore coupling was managed to provide **112**, leaving the "disarmed" OH free. Meanwhile in the left flask, an "armed-disarmed" coupling of thioglycosides **107** and **108** was carried out to give **111**. Mixing the mixtures in the two flasks followed by addition of another portion of the promoters (NIS/TfOH) afforded hexasaccharide **113** in a remarkable 53% isolated yield.



Scheme 19. OPG with orthogonal selenoglycoside (**86**) *vs.* thioglycoside (**87**).



Scheme 20. OPG synthesis of a diosgenyl saponin with orthogonal imidate (**90**) *vs.* thioglycoside (**91**).



Scheme 21. OPG synthesis of 1→6 linked trisaccharides with orthogonal phenylcarbonates (**94**) *vs.* thioglycosides (**95**).

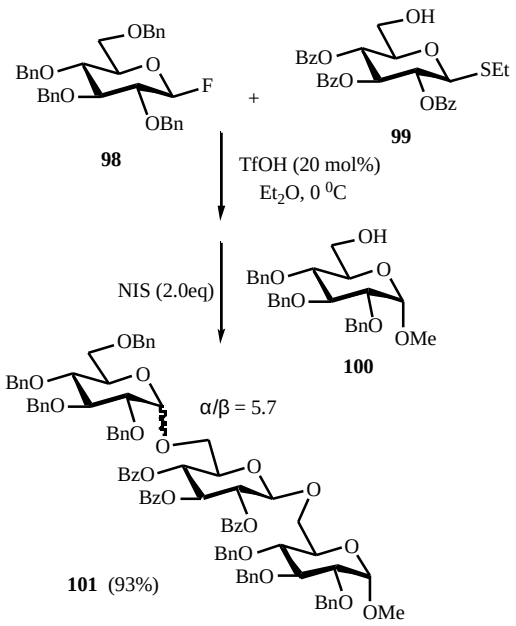
Valverde *et al*. employed the kinetic effect of an intramolecular *vs.* intermolecular coupling to achieve the OPG synthesis of the trisaccharide **117** (Scheme **25**) [50]. Thus the intramolecular glycosidation of **114** took place regioselectively on the 6-OH, then the second glycosidation of the 3-OH with the newly added donor **116** provided **117**.

Recently, Ning and Wang reported a facile OPG in the synthesis of the unique trisaccharide fragment of the Motif E of the *Mycobacterium tuberculosis* Cell Wall (Scheme **26**) [51]. The primary 6-OH of acceptor **118** was much active than the secondary 5-OH, therefore steering the OPG *via* a sequential addition of the two imidate donors (**119** and **120**) of a similar type.

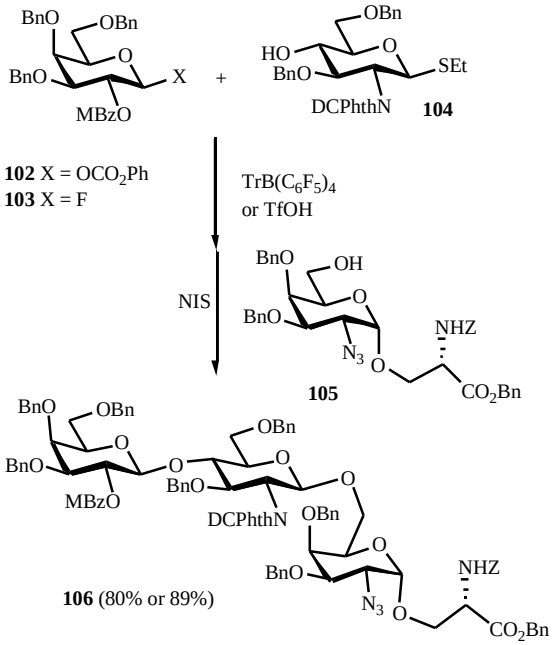
3.4 The Hybrid OPG

The first ever OPG protocol was reported by Kahne and Raghavan in 1993, which utilized the reactivity disparity of both the donors (sulfoxide **123** > sulfoxide **122**) and the acceptors (**124** with OH > **123** with TMS ether) (Scheme **27**) [9]. Thus, the sequential two-step OPG needs not to be controlled by a sequential addition of the coupling partner. Instead, three reactants (**122**-**124**) were mixed, upon addition of the promoter (TfOH), coupling between **123** and **124** took place faster, generating **125**, then a slow coupling between **122** and **125** produced **126**. A molar ratio of 3 : 2 : 1 for **122** : **123** : **124** was thus arranged that the decomposed donors **122** and **123** during the coupling were compensated.

Ley and coworkers combined the orthogonality and the armed-disarmed effect of donors for achieving the multi-step linear OPG synthesis of mannose tpye oligosacchrides [52-55]. A three-step OPG synthesis of the tetrasaccharide **133** was achieved in an unoptimized 10% yield, employing the orthogonal pairs of the fluoride **127**/selenoglycoside **128** and the intermediate selenoglycoside **131**/thioglycoside **132** and the armed-disarmed pair of the intermediate selenoside **129**/selenoside **130** for the successive glycosylation (Scheme **28**) [52]. Utilizing the similar strategy, a four-step OPG synthesis was also realized for the synthesis of the pentasaccharide **140** from five monosaccharide building blocks (fluorides **63**, **64**, selenosides **135**, **137**, and acceptor **139**) (Scheme **29**) [55].

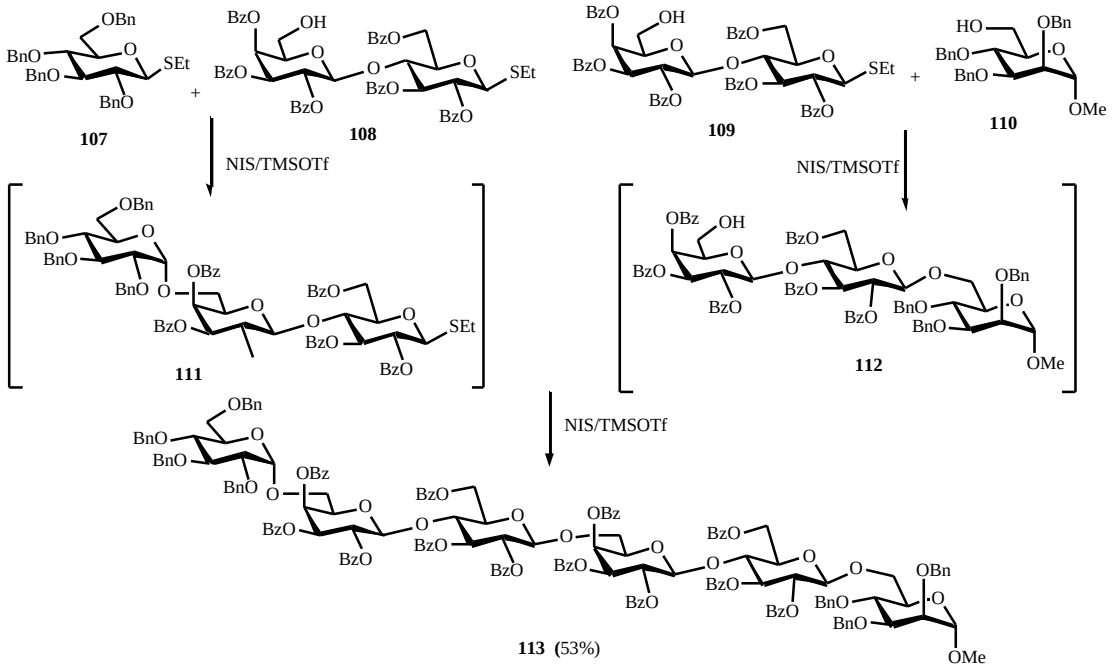


Scheme 22. OPG syntheses with orthogonal glycosyl fluoride (**98**) *vs.* thioglycoside (**99**).

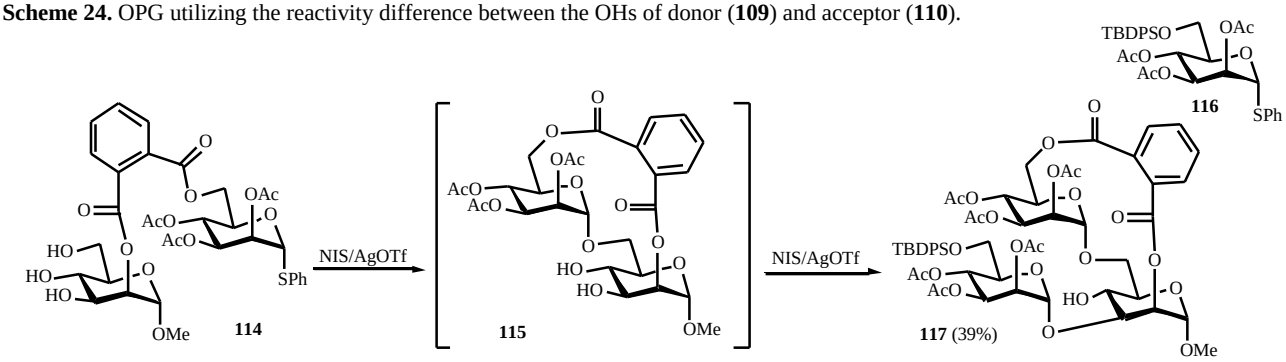


Scheme 23. OPG synthesis toward F1 α trisaccharide using orthogonal glycosyl carbonate (**102**) or fluoride (**103**) *vs.* thioglycoside (**104**).

In 1999, Takahashi and coworkers reported an OPG protocol for branched synthesis of oligosacchaides employing the combination of a pair of orthogonal bromide and thioglycoside donors and an acceptor with a pair of distinguishable OHs [56]. A representative example is depicted in Scheme 30. To the mixture of bromide **71** (1.05 eq), thioglycoside **142** (2.0 eq), and acceptor **141** (1.0 eq), AgOTf was added first to promote the coupling of **71** with



Scheme 24. OPG utilizing the reactivity difference between the OHs of donor (**109**) and acceptor (**110**).

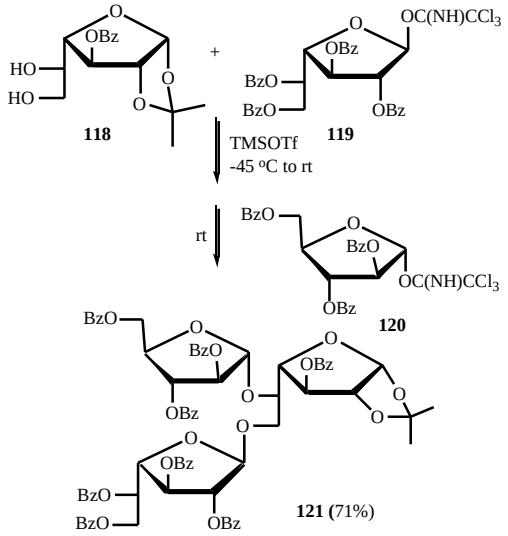


Scheme 25. OPG utilizing the reactivity difference of the OHs for an intramolecular *vs.* intermolecular coupling..

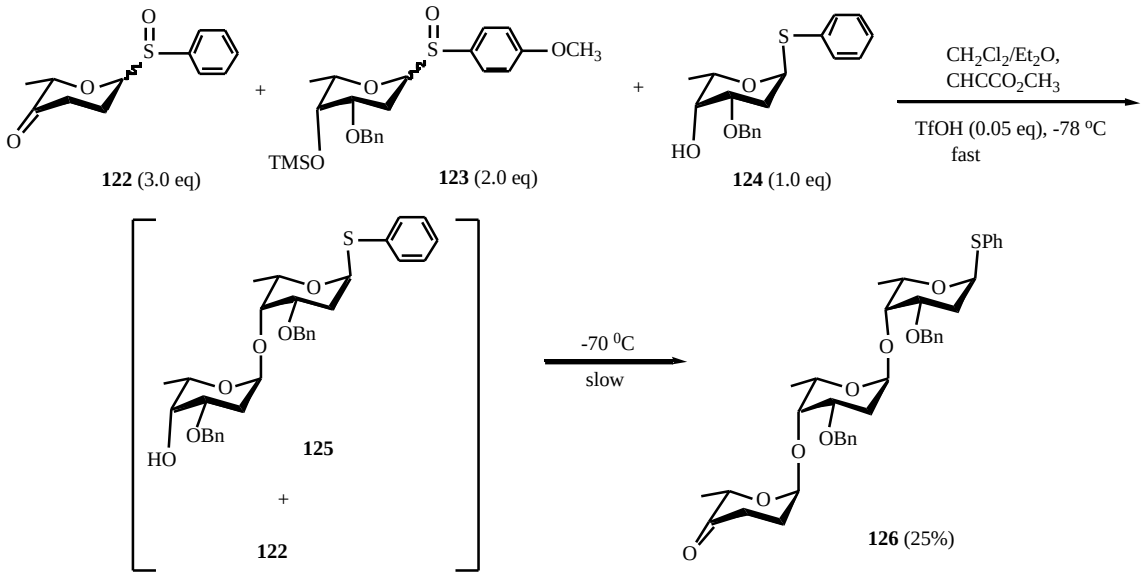
the active 6-OH, following addition of NIS/TfOH then activated **142** to couple with the remaining 3-OH.

Employing this strategy, together with the previous linear OPG with orthogonal donors, Takahashi *et al*. were able to build a library of 72 trisaccharides on a Quest 210^{TM} manual synthesizer [57]. The branched and linear type OPG were then combined in one pot for the synthesis of the heptaglucan of the phytoalexin elicitor [58]. A remarkable six-step OPG synthesis of this interesting glucan was achieved on the manual synthesizer (Scheme **31**) [59]. This is so far the OPG assembly coupling the highest number of saccharide building blocks. A little earlier, Muaiyama *et al.* employed four blocks for an OPG synthesis of this heptaglucan [60].

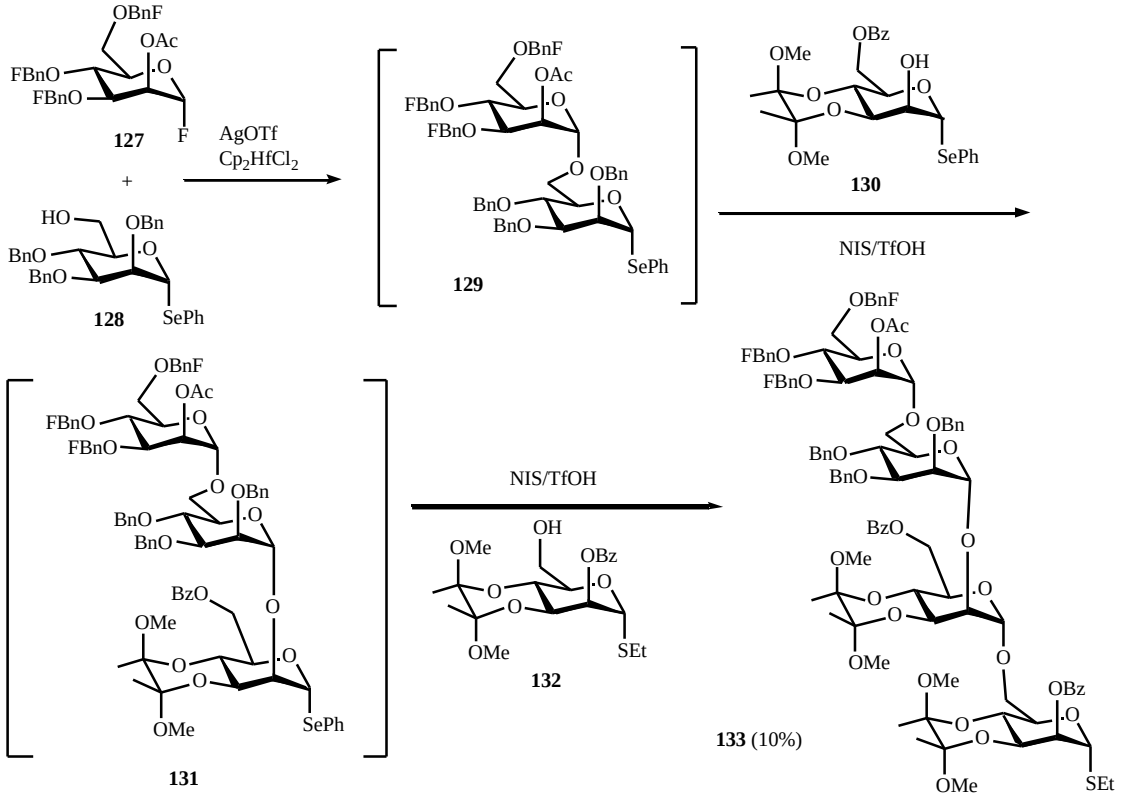
In 1999, we managed the synthesis of a bidesmosidic triterpene saponin using a novel hybrid OPG protocol (Scheme **32**) [61]. Where the trityl ester (on **151**) remained latent during the glycosylation of the 3-OH with imidate **152** at –60 ^{o}C, but conducted ready cleavage upon raising the temperature to rt. The resulting carboxylic acid **154** was then glycosylated with imidate **155** at 0 ^{o}C without additional



Scheme 26. OPG synthesis of the Motif E trisaccharide based on the reactivity difference of the two OHs of the acceptor (**118**).



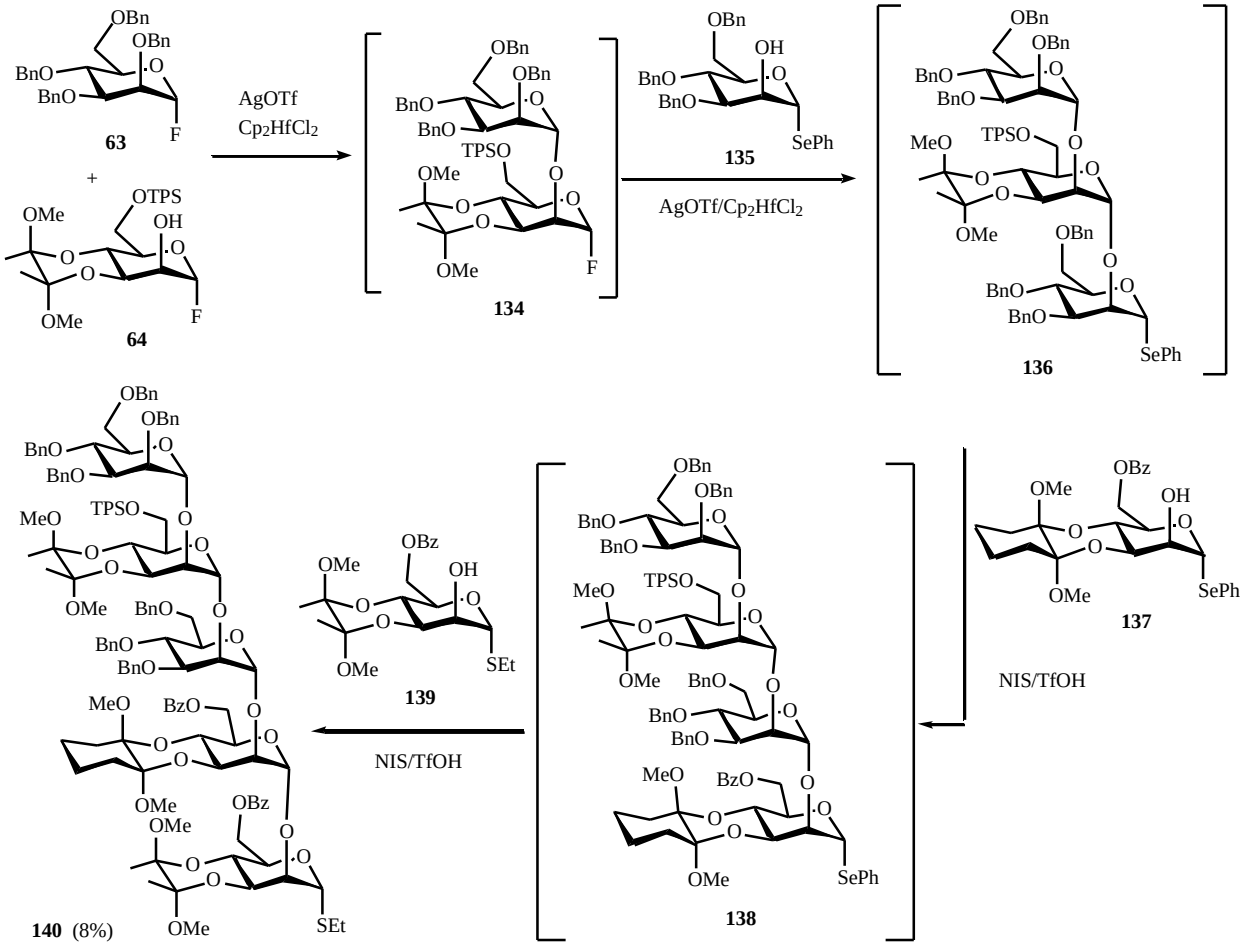
Scheme 27. OPG synthesis of the ciclamycin trisaccharide based on the reactivity disparity of both donors (**122**/**123**) and acceptors (**123**/**24**).



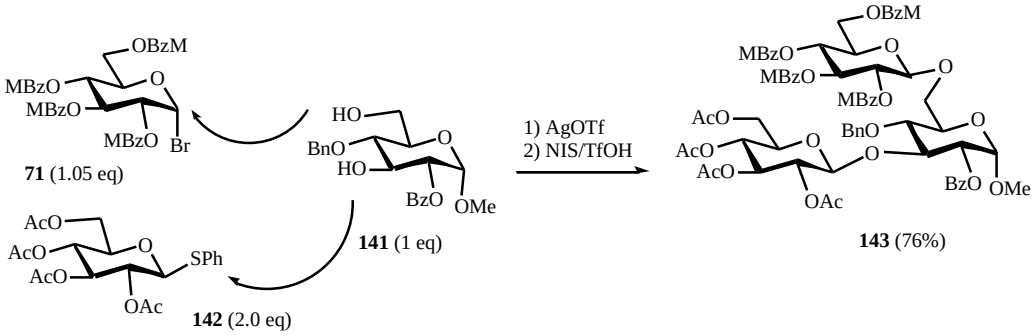
Scheme 28. A three-step OPG synthesis utilizing both orthogonal and armed-disarmed donors.

promoter. The trityl ether (on **155**) remained intact during the coupling, was directly glycosylated by thioglycoside **159**, prepared in another flask, to give the target molecule **160** in a satisfactory 62% yield. The use of two (or more) flasks provides another manual choice for controlling the OPG sequence.

Nearly 15 years, since the discovery of the armed-disarmed effect of donors, brings Fraser-Reid and



Scheme 29. A four-step OPG synthesis utilizing both orthogonal and armed-disarmed donors.

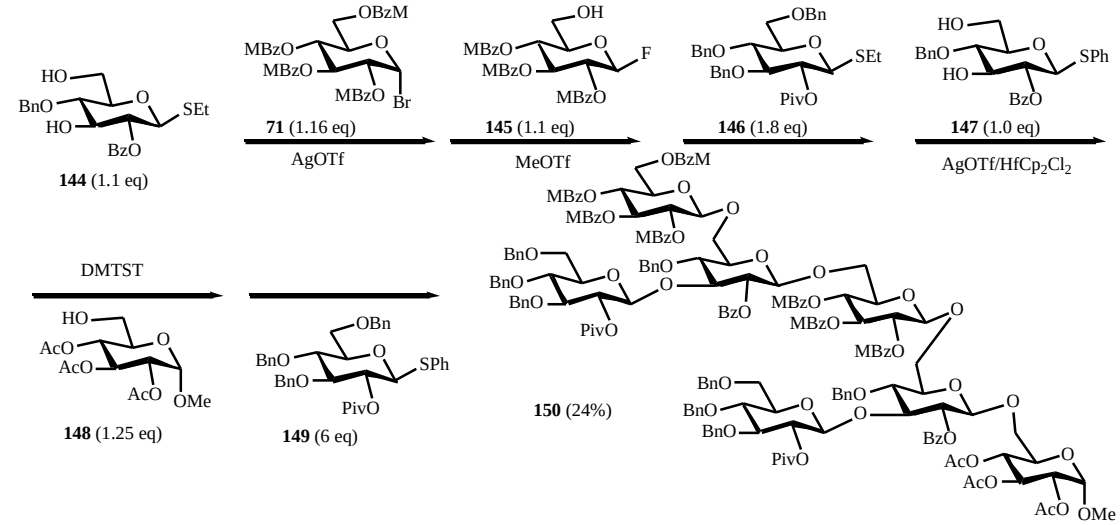


Scheme 30. A branched OPG employing the combination of orthogonal donors (**71**/**142**) and distinguishable acceptors (6- *vs.* 3-OH on **141**).

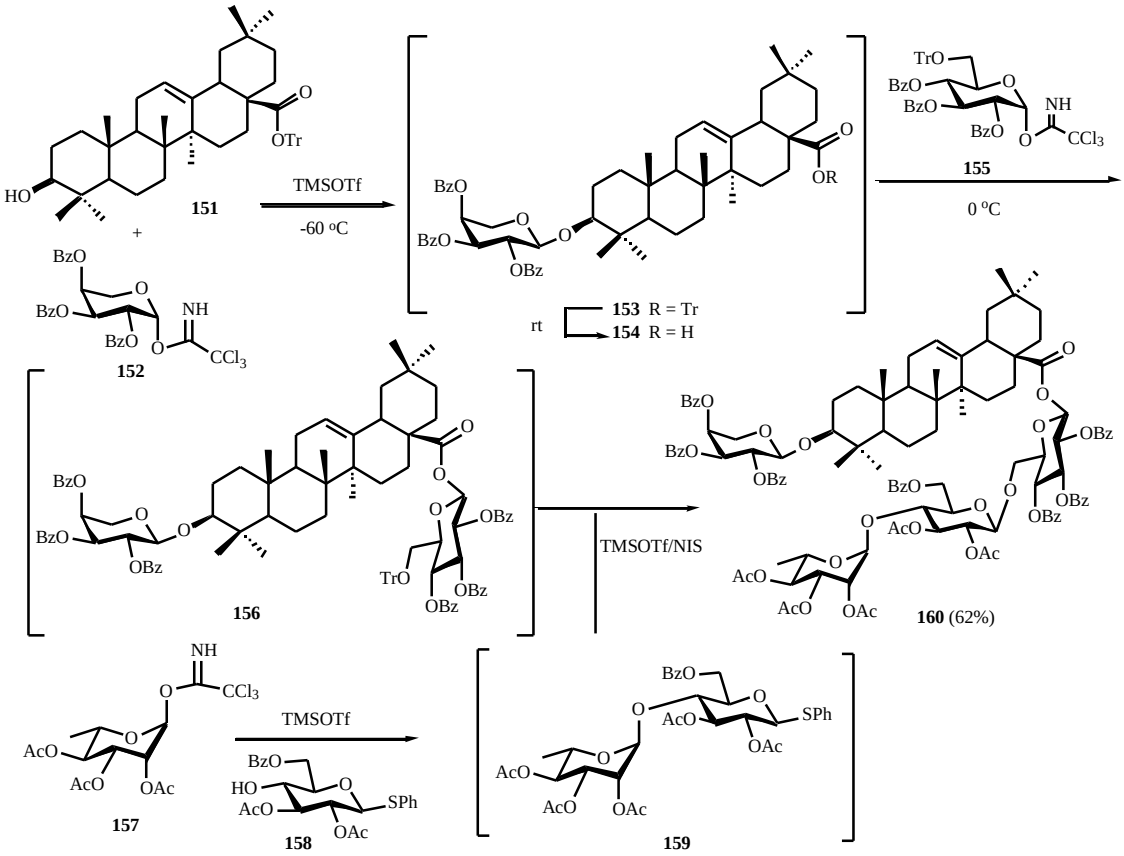
collaborators, in 2002, to a novel concept of reciprocal donor-acceptor selectivity (RDAS) [62]. In a RDAS-based OPG shown in Scheme **33**, a 1 : 1.3 : 1.3 mixture of diol **163**, *n*-pentenyl donor **162**, and *n*-pentenyl orthoester donor **161** was treated with NIS (2.5 eq)/BF_3OEt_2 (cat.), trisaccharide **164** and disaccharide **165** was obtained as the only products in 37% and 37% yields, respectively. The results indicate a reciprocal choice of donor **161** for the 3-OH and donor **162** for the 2-OH. However, a rational of these selectivities awaits further insight.

CONCLUSION

The last decade has witnessed the advent to fully development of the OPG procedures for the chemical synthesis of oligosaccharides. The influence of the armed-disarmed protecting groups, together with other structural

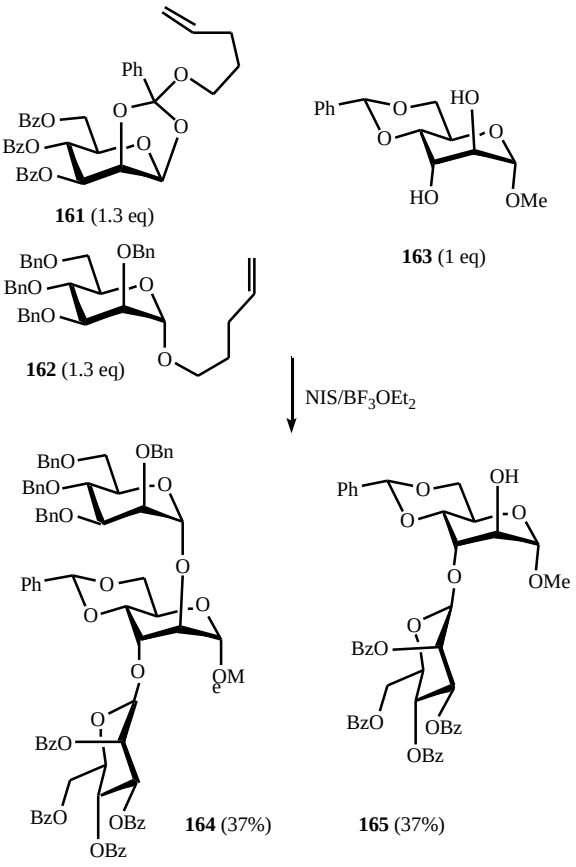


Scheme 31. A **six-step** OPG synthesis of the heptaglucan of the phytoalexin elicitor on a manual synthesizer.



Scheme 32. A two-flask hybrid OPG for the first synthesis of a bidesmosidic triterpene saponin.

factors, on the reactivity of glycosyl donors, are able to be quantified, thus a reactivity-based OPG could be programmable. The exploration of orthogonal leaving groups and the distinguishable acceptors has brought additional levels for sequential control of the OPG synthesis, thus multi-step OPGs become common practice. Addition sequence, temperature, solvent, as well as using separate flasks then mixing, provide external control for the OPG sequence. While the reciprocal donor-acceptor selectivity (RDAS) awaits further insight. The six-step OPG synthesis of the heptaglucan of phytoalexin elicitor on a manual synthesizer represents a height has been reached, and foresees the future trend, that the OPG procedure, which is performed in solution phase, might be an alternative for automation of the oligosaccharide synthesis, comparable to the solid phase methods for peptide and nucleotide synthesis.



Scheme 33. OPG using donors/acceptors with reciprocal selectivity.

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