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Superarmed and Superdisarmed Building Blocks in Expeditious Oligosaccharide Synthesis

Hemali D. Premathilake and

Department of Chemistry and Biochemistry, University of Missouri – St. Louis, One University Boulevard, St. Louis, MO 63121, USA

Alexei V. Demchenko

Department of Chemistry and Biochemistry, University of Missouri – St. Louis, One University Boulevard, St. Louis, MO 63121, USA

Alexei V. Demchenko: demchenkoa@umsl.edu

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 both the efficiency and yield. In contrast, expeditious strategies allow for the rapid chemical synthesis of complex carbohydrates by minimizing extraneous chemical manipulations. The armed–disarmed approach for chemoselective oligosaccharide synthesis is one such strategy that addresses these challenges. Herein, the significant improvements that have recently emerged in the area of chemoselective activation are discussed. These advancements have expanded the scope of the armed–disarmed methodology so that it can now be applied to a wider range of oligosaccharide sequences, in comparison to the original concept. Surveyed in this chapter are representative examples wherein these excellent innovations have already been applied to the synthesis of various oligosaccharides and glycoconjugates.

Keywords

Armed–disarmed strategy; Carbohydrates; Chemoselective activation; Expeditious synthesis; Glycoconjugates; Glycosylation; Oligosaccharides; Synthetic strategy

1 Introduction

1.1 Background

Complex carbohydrates (polysaccharides or complex glycoconjugates in which oligosaccharides are connected to peptides, proteins, or fatty acids) are involved in a variety of biological processes [1]. Throughout the past two decades, the main scientific effort in the field of glycoscience has remained centered upon those carbohydrates associated with diseases that consistently rank among the leading causes of death worldwide, such as cardiovascular disease, cancer, septicemia, bacterial, viral, and parasitic infections. The driving force behind this tremendous scientific and industrial effort is the belief that a comprehensive knowledge of the structural, conformational, and other general properties of these carbohydrates will help scientists understand the pathogenesis of the associated diseases. Consequently, this could lead to the development of new and effective strategies

for the prevention, diagnosis, and treatment of these diseases. Over the years, glycoscientists have mastered the techniques necessary for isolating only certain classes of naturally occurring carbohydrates. Therefore, the availability of pure natural isolates cannot satisfy all of the challenges presented by modern glycoscience. As a result, glycoscientists have turned to both chemical and enzymatic synthesis as a means for accessing complex carbohydrates. While enormous progress in the areas of synthetic, biological, and analytical chemistry has made many classes of organic compounds readily accessible through broadly applicable methods, carbohydrates of even moderate complexity still represent a significant challenge. A few representative examples of such oligosaccharide sequences are shown in Fig. 1.

1.2 Principles of Chemical O-Glycosylation

Poly- or oligosaccharide sequences are constructed by connecting monosaccharide units via O-glycosidic bonds. In nature this linkage is formed by a coupling reaction known as glycosylation, the course and selectivity of which is controlled by glycosyltransferases. In the chemical laboratory, glycosylation typically involves a promoter- (or activator)-assisted nucleophilic displacement, wherein a leaving group (LG = halogen, OH, *O*-alkenyl/imidoyl, *S*-alkyl/aryl/imidoyl, etc.) on the glycosyl donor is displaced by a hydroxyl moiety of the glycosyl acceptor (Scheme 1a) [2]. Remaining functional groups on both the glycosyl donor and acceptor are temporarily masked with protecting groups (P, T), which, along with strategies for their installation and removal (protection-deprotection), have become essential components of chemical syntheses of oligosaccharide molecules. Although protecting groups were initially applied to reduce unwanted side reactions by masking additional sites of reactivity, they can also affect the glycosylation in a variety of other ways; in other words, they “do more than protect” [3]. Since the anomeric center is chiral, particular care has to be taken with regard to the stereoselectivity of glycosylation. Despite the significant progress made in the area of glycoside synthesis [2], the necessity of forming either a 1,2-*cis*- or a 1,2-*trans*-glycosidic bond with high stereocontrol remains the main reason that chemical O-glycosylation is ranked among the most critical challenges of modern synthetic chemistry.

Although mechanistic rationalizations of the glycosylation reaction lack generality and consistency, and although studies dedicated to the reaction mechanism are still scarce, some conventions have already been well established [4]. For instance, in the case of ether-type non-participating substituents, glycosylation proceeds via a flattened oxacarbenium ion [5] (Scheme 1b), often leading to anomeric mixtures favoring 1,2-*cis* glycosides [6, 7] (for D-gluco/galacto series) due to the influence of the anomeric effect [8, 9]. Thus, variable factors such as temperature, pressure, structure, conformation, solvent, promoter, steric hindrance, protecting or leaving group are exceedingly important in influencing the stereoselectivity of glycosylation. Amongst these, neighboring group participation [10] is one of the most prominent effects dictating the stereochemical outcome of the glycosylation reaction (protecting groups do more than protect), as it is well established that 1,2-*trans* glycosides can be obtained from 2-acylated glycosyl donors. This selectivity arises from the acyloxonium intermediate formed as a result of the anchimeric assistance from the neighboring C-2 group (Scheme 1c).

1.3 Oligosaccharide Synthesis

The development of new leaving groups and efficient glycosylation methods is largely responsible for the progress that has been made in the area of oligosaccharide synthesis. When the arsenal of glycosylation techniques was limited to the Fischer (LG = OH) [11] and Koenigs–Knorr (LG = Cl, Br) [12, 13] approaches (or their variations) [14, 15], oligosaccharide assembly was limited to inefficient stepwise linear techniques. However, as more stable glycosyl donors, such as fluorides [16], thioglycosides [17], and *O*-alkenyl

glycosides were developed [18], the possibility of selective and/or chemoselective activation of one leaving group over another emerged. In linear oligosaccharide synthesis, the disaccharide product formed from the single step glycosylation reaction (see Scheme 1) is then converted into either a second-generation glycosyl acceptor or donor; this is accomplished via the liberation of a specific hydroxyl group or installation of a suitable leaving group, respectively (Scheme 2). These second generation disaccharide building blocks are then allowed to react with an appropriate monosaccharide glycosyl donor or acceptor, resulting in the formation of a trisaccharide. The protecting/leaving group manipulation and glycosylation sequence can be then reiterated until an oligosaccharide of the desired chain length is obtained.

It soon became apparent, however, that both the linear and convergent [19–21] approaches were too inefficient, due to the extensive protecting or leaving group manipulations between each glycosylation step. Consequently, the past two decades have witnessed a dramatic improvement of the methods and strategies used for oligosaccharide synthesis, as scientists have persistently aimed to answer the key question: can oligosaccharides be obtained more expeditiously through the elimination of these unnecessary synthetic steps? The first attempts to address this challenge emerged in the mid-1980s and 1990s, which resulted in the development of a number of revolutionary approaches. Many of these innovative strategies involve selective activations, wherein different leaving groups are sequentially activated, minimizing the need for protecting group manipulations between glycosylation steps; selective activation [19, 22], two-step activation [19, 23–25], and the active-latent concept [26–29] are just a few classifications of such approaches. One specific example, the orthogonal approach, makes use of two chemically distinct glycosyl donors, wherein one of the leaving groups is selectively activated while the other remains intact, and vice versa, offering significant flexibility [30]. This activation sequence can then be reiterated to give straightforward access to larger oligosaccharides.

Another direction in expeditious oligosaccharide synthesis emerged with the discovery of the so-called armed–disarmed approach by Fraser-Reid and coworkers [31]. This strategy, based on the chemoselectivity principle, utilizes only one class of leaving group; thus, glycosyl donor reactivity is modulated entirely through the choice of protecting group (protecting groups do more than protect). This effect allows for direct chemoselective coupling between an activated (armed) glycosyl donor and a deactivated (disarmed) glycosyl acceptor, and the resulting disaccharide can then be used directly in subsequent glycosidation.

With the main focus on the armed–disarmed concept, this chapter discusses the recent progress that has been made in the area of chemoselective oligosaccharide synthesis. The classic *armed–disarmed approach*, developed by Fraser-Reid, has created a solid basis for extensive studies and applications, and all strategies discussed in this chapter are directly related to (or derived from) this elegant concept. As recent improvements have significantly expanded the scope of the original chemoselective concept, a series of building blocks, the reactivity of which extends beyond the traditional armed–disarmed definition, have additionally been introduced. These “superarmed” and “superdisarmed” building blocks have helped to expand the scope of the original methodology so that it can now be applied to the synthesis of a much broader range of complex oligosaccharide sequences, in comparison to that of the classic armed–disarmed concept. These excellent innovations have already been applied to the synthesis of various oligosaccharides and glycoconjugates, and some representative examples are presented herein.

2 Armed–Disarmed Strategy for Oligosaccharide Synthesis

The chemoselective approach and its variations discussed in this section make use of only one class of leaving group for both reaction components, which are either activated (armed donor) or deactivated (disarmed acceptor) by the influence of the protecting groups (R_1 , R_2 , Scheme 3). Usually, the protecting groups in both reaction components have to be taken into consideration to allow for direct chemoselective activation of the armed glycosyl donor over the disarmed glycosyl acceptor. As both components bear the same type of LG, the key factor for an armed–disarmed activation to take place is finding suitable reaction conditions that can efficiently differentiate between the activated and deactivated building blocks. In most cases, the differentiation is achieved by the choice of promoter, temperature, or solvent [32].

As already mentioned, the majority of strategies discussed in this subsection allow for efficient oligosaccharide assembly without the need to perform additional synthetic steps between the glycosylation steps. Accordingly, the disarmed leaving group of the resulting disaccharide can be activated directly, although a more powerful promoter or elevated temperatures are typically required.

2.1 Classic Concept: Electron-Withdrawing Substituents and the Synthesis of *cis*–*trans*-Patterned Oligosaccharides

Although the effect of protecting groups on reactivity had been noted [20], it was Fraser-Reid who described, in 1988, a new manner by which the differential properties of protecting groups could be exploited, termed the “armed–disarmed strategy” [33]. It was noticed that ester-type protecting groups (OAc, OBz, etc.) strongly reduced, i.e., “disarmed,” the reactivity of the *n*-pentenyl glycosyl donor, in comparison to that of its alkylated (benzylated, OBn) “armed” counterpart.

One justification for such an observation is that the increased electron-withdrawing ability of ester protecting groups decreases the electron density (nucleophilicity) of the anomeric heteroatom, which translates into a diminished ability to interact with the electrophilic promoter. As a result, the armed leaving group reacts faster, with the disarmed leaving group reacting either much more slowly or not at all. In order to achieve an efficient differentiation in reactivity, mild promoters have an advantage, as they are able to offer a more controlled activation. For example, iodonium(di- γ -collidine)perchlorate (IDCP) was found to be a suitable mild electrophilic activator for *O*-pentenyl glycosyl donor **1**, and corresponding disaccharide **3** was isolated in 62% yield (Scheme 4) [33]. As the anomeric configuration of the product is influenced by the protective group at O-2, a 1,2-*cis*-linked disaccharide is preferentially obtained in the first step, due to the use of the non-participating, ether-type (*O*-benzyl) arming substituent.

Furthermore, the leaving group of disarmed building blocks (such as **2** or **3**) can also be activated, but this would typically require more time, higher temperature, and/or stronger promoters. For instance, the direct glycosidation of disaccharide **3** was readily achieved in the presence of a strong promoter system, NIS/TfOH. This glycosylation step was performed with glycosyl acceptor **4**, resulting in the stereo-selective formation of a 1,2-*trans* glycosidic linkage. As mentioned before, glycosidation of 2-acylated glycosyl donors typically proceeds via the formation of the bicyclic acyloxonium intermediate, which coordinates the 1,2-*cis* face of the ring. As a result of this two-step activation sequence, a *cis*–*trans*-patterned trisaccharide (**5**) is obtained, wherein the monosaccharide units are sequentially connected via a 1,2-*cis* and 1,2-*trans* linkage (Scheme 4).

Although this discovery was made using *n*-pentenyl glycosides, this electronic effect ultimately proved to be of a general nature, and as such can be applied to nearly any class of glycosyl donor. This concept was further explored for the chemoselective glycosidations of thioglycosides [34], selenoglycosides [35], fluorides [36], phosphoramidates [37], substituted thioformimidates [38], glycals [39], and thioimidates [40, 41]. The usefulness of this approach was realized in application toward expeditious oligosaccharide synthesis, as it circumvents the need for protecting group manipulations at the anomeric center [42].

2.2 Strategic Updates to the Original Armed–Disarmed Method

Synthesis of the *cis*–*cis*-Patterned Oligosaccharides Using Reprotection of the Intermediate Disaccharide—To address the major limitation that the armed–disarmed strategy could only be applied to the synthesis of oligosaccharides having a *cis*–*trans* glycosylation pattern, van Boom and co-workers designed a method whereby the synthesis of *cis*–*cis*-linked derivatives could also be achieved [34]. In the first synthetic step the classic armed–disarmed activation was performed; however, the resulting disaccharide was then reprotected (OBz → OBn) prior to subsequent glycosidation. A representative example of this strategy is shown in Scheme 5.

Armed thioglycoside donor **6** was selectively activated over disarmed glycosyl acceptor **7** in the presence of IDCP to provide the disarmed 1,2-*cis*-linked disaccharide (**8**) in 91% yield. The latter was then subjected to a two-step debenzoylation-benzylation sequence, whereupon the resulting disaccharide donor (**9**) was glycosidated with disarmed acceptor **7**, to afford the *cis*–*cis*-linked trisaccharide (**10**) in 72% yield. The conversion of the second generation glycosyl donor **8** into the armed state **9** also allowed for the second coupling step to be performed with the mild promoter IDCP.

Synthesis of *trans*–*trans* Patterned Oligosaccharides Using Picolinyl Arming Participating Group—Demchenko et al. [41] demonstrated that with the use of an *O*-picolyl substituent as an “arming participating group” at C-2 of the glycosyl donor, a 1,2-*trans* glycosidic linkage can be chemo- and stereo-selectively introduced in the first glycosylation step. For example, glycosidation of armed glycosyl donor **11** with disarmed acceptor **12** in the presence of Cu(OTf)₂, produced 1,2-*trans*-linked disaccharide **13** in 74% yield (Scheme 6). Due to the opposite stereo-chemical outcome of this glycosylation, in comparison to the 1,2-*cis* linkage formed in the first step of the classic armed–disarmed approach, this approach was called the *inverse armed–disarmed* strategy. Subsequent glycosidation of disarmed disaccharide **13** with the standard glycosyl acceptor **14** could then be achieved in the presence of a more powerful activator AgOTf, and the resulting *trans*–*trans*-linked trisaccharide **15** was obtained in 88% yield [41]. NMR experiments were utilized, showing the presence of the anticipated cyclic compound **A** as the key reaction intermediate (Scheme 6).

2.3 Conceptual Updates to the Original Armed–Disarmed Method

Deactivation by a Remote Protecting Group Capable of Powerful Electron-Withdrawal—Madsen et al. [43] clearly demonstrated that a single electron-withdrawing moiety at the remote C-6 position will sufficiently disarm the leaving group of a glycosyl acceptor, in comparison to the per-alkylated glycosyl donor. This effect was especially pronounced with the use of a pentafluorobenzoyl (PFBz) ester, capable of a very powerful electron-withdrawal [44]. For example, armed benzylated thioglycoside **16** could be chemoselectively activated over the disarmed 6-*O*-pentafluorobenzoyl acceptor **17** in the presence of NIS/TESOTf to provide disaccharide **18** (Scheme 7). The latter could then be glycosidated with glycosyl acceptor **19** in the presence of NIS/TESOTf to give trisaccharide **20** in 61% yield. It is important to highlight that this approach allows for the *cis*–*cis*

oligosaccharide sequence to be obtained directly, without deprotection/reprotection of the intermediate disaccharide, as previously discussed for the synthesis reported by van Boom (see Scheme 5).

Crich et al. [45] also investigated the influence of the electron-withdrawal at the C-6 position on the reactivity of glycosyl triflates and stereoselectivity of their glycosidations. In exploring a series of mono-, di-, and tri-fluorinated 6-deoxy rhamnosides, a clear correlation between the strength of electron-withdrawal at C-6 and stability of the anomeric triflates was established. While common rhamnosyl triflates undergo rapid decomposition at temperatures above -60°C , it was shown that their 6,6,6-trifluorinated counterparts remained stable at temperatures up to $+10^{\circ}\text{C}$. Many related studies have further demonstrated that the arming/disarming effect of the protecting groups may also be highly dependent upon their location (see Schemes 11 and 12), geometry, and core donor structure [46, 47].

Deactivation with Cyclic Ketals/Acetals: Torsional and Electronic Effects—

Fraser-Reid and co-workers discovered that the deactivation of glycosyl donors could also be achieved through the strategic placement of cyclic acetal/ketal substituents that would lock the pyranose ring in the ${}^4\text{C}_1$ chair conformation. This type of deactivating effect was attributed to the increased rigidity of the fused ring system, prohibiting the oxacarbenium ion intermediate from achieving the requisite planar geometry about the (C-2)-(C-1)-(O-5)-(C-5) atoms [48]. As depicted in Scheme 8, in a series of *O*-pentenyl glycosides, reactivity was noted to increase from the tricyclic 2,3:4,6-diacetone ketal **21** to the bicyclic 4,6-benzylidene acetal **22** with the traditional armed *O*-pentenyl glycoside (**1**) being the most reactive. This relative reactivity trend was proven by direct chemoselective activation of armed glycosyl donor **1** over benzylidene-protected glycosyl acceptor **23**. As in the case of the traditional armed–disarmed approach, IDCP was found to be a suitable promoter that allowed for efficient differentiation of the reactivity levels between the armed and torsionally disarmed building blocks (**1** and **23**, respectively). As a result, disaccharide **24** was isolated in 52% yield, with no observed by-products resulting from the self-condensation of glycosyl acceptor **23**. These results suggested that the disarming could be achieved by acetal/ketal protecting groups exclusively.

This concept was expanded upon by Ley and co-workers, who clearly demonstrated that similar deactivation could be effectively achieved with the use of a variety of cyclic 1,2-diacetal/diketal systems [49]. And the example below highlights one such application, in which a two-step sequential activation was accomplished using a one-pot synthetic strategy. The one-pot approach allows for two (or more) sequential glycosylation reactions to be performed in a single flask (pot) without isolation and purification of the intermediate [50]. Thus, armed glycosyl donor **25**, of the L-rhamno series, was chemoselectively activated over torsionally disarmed rhamnosyl acceptor **26** in the presence of NIS/TfOH (Scheme 9). The resulting disaccharide (**27**, not isolated) was then reacted directly with rhamnosyl acceptor **28**, and the final trisaccharide **29** was isolated in 62% yield over the two-step activation sequence. Clearly, one-pot strategies offer the fastest pathway to oligosaccharides, although to ensure successful isolation of the final product, all steps need to proceed with particularly high diastereoselectivity and yield [50, 51].

It should be noted, that the ester and acetal/ketal groups disarm building blocks following different considerations and mechanisms. Whereas ester disarming effect is purely electronic, benzylidene/isopropylidene groups were initially assumed to disarm exclusively through torsional strain. In further mechanistic probing, Bols and co-workers proposed that the disarming effect of the 4,6-acetal may also be due to the orientation of the electron-withdrawing C-6 substituent [52]. From a series of model experiments, it was found that a

basic torsional disarming effect does exist; however, the data suggested that the substituent configuration (stereoelectronic effect) also plays a significant role in the overall degree of disarming. For example, the reactivity of torsionally disarmed compound **32** (with an axially oriented 6-methoxy substituent) falls between that of per-methylated armed building block **33** and compounds **30/31** (in which the equatorially oriented 6-O-substituents are capable of more a geometrically directed electron-withdrawal, Fig. 2). Based on relative rates of hydrolysis (Fig. 2), it was concluded that conformational restriction and stereoelectronics (charge-dipole interactions) were almost equally responsible for the observed disarming effect.

2.4 Going Beyond the Simple Armed and Disarmed Building Block Combination

Many Different Reactivity Levels Revealed—Further progress in the area of chemoselective oligosaccharide synthesis emerged with the development of a programmable oligosaccharide strategy, which stemmed from the studies pioneered in Fraser-Reid's, van Boom's, Ley's, and Wong's groups. Subsequently, attempts to classify, and even predict, the outcome of a glycosylation reaction (or a sequence) led to the further development of approaches that attempted to quantify the reactivity of building blocks [46–48, 53, 54]. Following Fraser-Reid's study on the *n*-pentenyl glycoside-based methodology for determining the relative reactivities of variously protected pairs of glycosides [53], Ley et al. developed an approach wherein building block reactivity could be “tuned” [46]. In a series of competitive experiments, wherein two glycosyl donors were competing for one glycosyl acceptor, a series of relative reactivity ratios was established. Additionally, these ratios were found to correspond to various protecting group patterns. For instance, an important relationship between the position of benzoyl groups and their effect on reactivity surfaced from these studies (Scheme 10).

Thus, the greatest disarming effect was seen from the 2-benzoyl substituent in compound **37**, followed by the 4-benzoyl and 3-benzoyl substituents (in compounds **34** and **35**, respectively). In addition, cyclic ketal **36** was found closer in reactivity to the mono-benzoylated rather than the di-benzoylated series of compounds. Not surprisingly, reactivity levels recorded for the mono-benzoylated (**34**, **35**, **37**), di-benzoylated (**38–40**), and torsionally disarmed (**36**) glycosyl donors fell in between the traditional per-benzoylated armed rhamnoside **25** and its disarmed per-benzoylated counterpart **41**.

Wong et al. devised a mathematical approach, assigning relative reactivity values (RRVs) to a wide library of building blocks [47]. The determination of RRVs was made in standardized reaction conditions, tolyl thioglycoside donors in the presence of an NIS/TfOH promoter system. The cumulative reactivity data was then compiled into a predictive computer program called Optimizer [47]. Various intermediate reactivity levels were revealed during these studies, with nearly all compounds clearly situated between the armed (**42**) and disarmed (**48**) building blocks (Scheme 11). Similar to Ley's findings, the acetal-protected building blocks were also positioned between the armed and disarmed building blocks, being closer in reactivity to the former. For example, 4,6-benzylidene-2,3-dibenzoyl derivative **47** was approximately 50 times more reactive than its per-benzoylated disarmed counterpart **42** (Scheme 11).

Following these studies, a well-rounded technology for one-pot oligosaccharide synthesis based on RRVs emerged. A representative example is depicted in Scheme 11, wherein armed glycosyl donor **48** was chemoselectively activated over glycosyl acceptor **52** in the presence of NIS/TfOH. The resulting disaccharide intermediate was then reacted with added disarmed glycosyl acceptor **43** to form a trisaccharide intermediate that was then glycosidated with added glycosyl acceptor **53** to provide tetrasaccharide **54** in 39% overall yield [47]. The reactivity difference between similarly protected sugars of different series

has also to be taken into consideration. For example, the reactivity ratio between perbenzylated tolyl thioglycosides of the 6-deoxy-L-*galacto*, D-*galacto*, and D-*gluco* series was found to be 27.1/6.4/1 respectively [47]. Ley's studies also showed a similar correlation between the reactivity of building blocks of different series [49, 55]. Accumulation of comparison data for reactivity of building blocks of 2-amino-2-deoxysugars and their neutral counterparts has also began to emerge [54, 56–60].

3 Superdisarmed Building Blocks

Although most reactivity levels in Fraser-Reid's, Ley's, and Wong's studies fall between the traditional armed and disarmed building blocks, Wong's study revealed a number of building blocks that were extended beyond this boundary. For example, 2-hydroxyl galactoside **51** was found to be three times more reactive than the traditional armed galactoside **48** (Scheme 11). Indirectly, this discovery opened up a new avenue for studying building blocks that are either more reactive than armed ones (superarmed) or less reactive than disarmed ones (superdisarmed); the studies arising from these two directions are surveyed below. In this section, those building blocks possessing a lower reactivity than their conventional per-acylated (per-benzoylated) disarmed counterparts will be discussed.

3.1 Superdisarming by Torsional Effect

As mentioned before, Fraser-Reid [48], Ley [61], and Bols [52] found that anomeric deactivation can be achieved by the combination of the torsional and electronic effects of cyclic acetal/ketal protecting groups. The combination of two separate effects could lead one to believe that such systems would be less reactive than the pure-electronically disarmed, acylated building blocks. However, in the majority of cases investigated and surveyed in the previous section, the acetal/ketal-protected derivatives were found to be of intermediate reactivity, falling between the traditional armed and disarmed building blocks (see Schemes 10 and 11). It was not until more recent studies by Boons [62] that it became apparent that thioglycosides protected with the cyclic 2,3-carbonate group could be even less reactive (superdisarmed) than traditional disarmed acylated derivatives. The following example clearly illustrates this finding. Thus, disarmed per-benzoylated thioglycoside donor **55** was chemoselectively activated over superdisarmed glycosyl acceptor **56** in the presence of NIS/TMSOTf (Scheme 12).

Along similar lines, Demchenko et al. performed the direct chemoselective activation of the electronically disarmed SBox glycoside **58** over torsionally/electronically disarmed (superdisarmed) glycosyl acceptor **59**. This direct chemo-selective coupling resulted in the formation of disaccharide **60**, proving that even traditional benzylidene systems can superdisarm building blocks of the SBox series. It appears that there is a certain inconsistency between this result and the comprehensive programmable approach which showed benzylidene derivatives to be more reactive than their disarmed counterparts. Although a direct investigation of these two findings is not yet available, studies reported by Bols [63] offer the explanation that the disparity could be simply explained by the benzylidene orientation; axial –galactose (Wong et al.) vs equatorial – glucose (Demchenko et al.).

In order to access the electronic effects of various ring substituents, Bols et al. designed the following model study which showed equatorial substituents to be significantly more electron-withdrawing (destabilizing, disarming) than their axial counterparts (Fig. 3). The values shown are in pH units, and reflect the amount by which the pKa of the substituted amine decreases with respect to piperidine. It is believed that this result can help to rationalize different relative reactivity found amongst 4,6-benzylidene building blocks of different series (gluco vs galacto in this case). However, a more systematic study of this

phenomenon, and perhaps a series of side-by-side chemoselective coupling experiments, would be needed to draw a more direct conclusion.

3.2 Superdisarming by Electronic Effects

Demchenko et al. also reported that a mixed protecting group pattern can unexpectedly and profoundly affect the glycosyl donor reactivity [40]. Upon investigating *S*-benzoxazolyl (SBox) glycosides containing an “arming” benzyl group at C-2 and “disarming” acyl groups at the remaining hydroxyls, it was expected that reactivity would fall somewhere between that of the armed (per-benzylated) and the disarmed (per-benzoylated) glycosyl donors; similar to the results found in Ley’s studies for building blocks of the L-rhamnose series, as discussed above. However, the results acquired with the SBox glycosides of the D-glucose series revealed that these “mixed-patterned” glycosyl donors were the least reactive amongst the building blocks investigated (Table 1) [40].

Thus, the reaction of armed SBox donor **61** with glycosyl acceptor **63** in the presence of copper(II) trifluoromethanesulfonate proceeded smoothly, and product **64** was isolated in a good yield of 89% (Entry 1, Table 1). Along similar lines, it was discovered that disarmed perbenzoylated SBox glycoside **58** also reacted readily, although this glycosylation was marginally slower in comparison to that of the armed per-benzylated building block **61**, never fully going to completion, resulting in a slightly lower, 70% yield of the disaccharide **65**. Interestingly, when essentially the same reaction conditions were applied to the glycosidation of 2-*O*-benzyl-tri-3,4,6-*O*-benzoyl protected SBox glucoside **62**, no formation of the expected disaccharide **66** was detected.

As Lemieux’s halide stability theory [64–66], Fraser-Reid’s armed–disarmed concept rationale [31, 33], Ley’s tuning reactivity studies [46], and Wong’s programmable oligosaccharide synthesis [47] all predicted 2-*O*-benzylated glycosyl donor **62** to be more reactive than its per-benzoylated counterpart **58**, these unanticipated results necessitated further studies. This finding implies that a combination of electronic effects, beyond the recognized inductive effects of the C-2 protecting group, may exist. The observed reactivity pattern was rationalized by the occurrence of the so-called “O-2/O-5 Cooperative Effect” [40]. Thus, in addition to the “arming/disarming” nature of the protecting group at O-2, stabilization of the glycosyl cation intermediate must also be taken into consideration. First, this stabilization can be achieved from the lone electron pair on the neighboring endocyclic ring oxygen (O-5) as in the armed glycosyl donor **A**, shown in Fig. 4. However, if electron-withdrawing protecting groups are placed near the O-5 ring oxygen (C-4 and C-6, as in the disarmed donors **B** or **C**), the electron density on O-5 will be decreased, effectively suppressing oxacarbenium ion formation. In this case, the ability of the system to stabilize via other plausible internal modes may become increasingly important.

A second type of stabilization may arise based on the availability of the lone electron pair on an acyl type protecting group at O-2, which is capable of providing stabilization via the formation of an acyloxonium ion intermediate, as in disarmed glycosyl donor **B**. Crich et al. [67] emphasized that the anchimeric assistance was particular to the 1,2-*trans* orientation of the 2-*O*-acyl and 1-SBox leaving group, as stabilization presumably takes place via the concerted displacement of the leaving group. However, if no source of secondary stabilization is available, as in case of 2-*O*-benzyl substituent in **C**, this combination will give rise to the overall “superdisarming” protecting group pattern.

4 Superarmed Building Blocks

In contrast to superdisarmed building blocks, possessing reactivity even lower than that of the peracylated disarmed building blocks, other, super reactive glycosyl donors have also

been discovered. The term superarmed was first coined by Bols for describing the reactivity of conformationally armed building blocks. Herein, however, we apply the term superarmed to all building blocks that are more reactive than conventional per-alkylated armed building blocks.

4.1 Superarming by Conformational Effects

As was previously noted, the substituent orientation can have a strong effect on the reactivity of a molecule. A model study of the relative pK_a values for protonated heterocyclic amines showed that equatorial substituents are significantly more deactivating than their axial counterparts (compare **67** and **68** in Fig. 5) [63]. Further revealed by these findings was that a perturbation of the equilibrium between ring conformations may also occur upon protonation of the heterocyclic amine [68]. This was found to result from the desire for substituents to reside axially, as they have a greater ability to provide charge stabilization through charge-dipole interactions. For example, cyclic amine derivative **68** was found to exist predominantly in the conformation wherein the electron-withdrawing hydroxyl substituents are axial. This study further suggests that positively charged oxocarbenium ion intermediates may also spontaneously undergo conformational changes in an attempt to maximize the number of axial substituents. If so, this conformational change would be made easier if the starting material already had a number of axial substituents [69]; for example, galactose has long been known to be more reactive than glucose (compare hydrolysis rates for compounds **69** and **70**, Fig. 5).

Furthermore, when conformationally restricted 3,6-anhydroglucoside **71**, having all-axial hydroxyl groups, was investigated, it was shown to hydrolyze much faster than its all-equatorial counterpart **69** [70].

This result implies that if all-equatorial glucosyl donors were converted into their all-axial counterparts, the reactivity could be dramatically increased. Based on the knowledge that steric congestion at the equatorial C-3 and C-4 positions causes conformational changes [71, 72], Bols and co-workers were able to exploit this phenomenon [70, 73, 74]. However, when TBS protection was applied to glucose derivative **72**, the product **73** was found to exist in more of a skew-boat conformation [75] (Scheme 13) rather than the anticipated 1C_4 conformation adopted by analogous xylopyranose derivatives [76], perhaps due to the added steric bulk of the substituent at C-5. Nevertheless, a sufficient conformational change was induced, reconfiguring the substituents perpendicular to the sugar ring. As such, this conformationally superarmed glucosyl donor **73** showed a dramatic 20-fold increase in reactivity, relative to the traditional armed benzylated derivatives, as shown by direct competition experiments [73]. Furthermore, superarmed glycosyl donor **73** could be successfully coupled with “armed” acceptor **74** to afford the resulting disaccharide **75** in 85% yield [77]. Similar observations have also been made with glycosyl donors of the manno, rhamno, and galacto series [74].

Interestingly, Bols et al. showed that while the 4,6-dialkylsilylene protection disarms the glycosyl donor, the 3,6-dialkylsilylene tethering is able to arm glycosyl donors [77]. As a matter of fact, the axial-rich 3,6-tethered glycosyl donor demonstrated superarming properties that have been proven in the direct competition experiments with traditional armed glycosyl donor [77].

4.2 Superarming by Electronic Effects

As mentioned before, a mixed protecting group pattern could unexpectedly and profoundly affect glycosyl donor reactivity [40]. Along these lines, a glycosyl donor containing a participating benzoyl group at C-2 and electron donating groups at the remaining positions

was also investigated. Interestingly, these glycosyl donors proved to be even more reactive (superarmed) than their armed per-benzylated counterparts [78, 79]. Thus, the reaction of armed SBox donor **61** with glycosyl acceptor **14** in the presence of dimethyl(thiomethyl)sulfonium trifluoromethanesulfonate (DMTST) proceeded smoothly, and product **77** was isolated in 91% yield (Entry 1, Table 2). Furthermore, it was discovered that the disarmed perbenzoylated SBox glycoside **58** failed to react under essentially the same reaction conditions. Unexpectedly, the glycosidation of 2-*O*-benzoyl-tri-3,4,6-*O*-benzyl protected SBox glucoside **76** proceeded almost instantaneously, and disaccharide **78** was obtained in 90% yield (for comparison, the glycosidation of armed donor **61** took 2 h).

The reactivity of the superarmed donors was illustrated in a direct competitive glycosylation experiment, wherein both the superarmed and armed donors (**76** and **61**, respectively), were placed in the same reaction vessel with glycosyl acceptor **14**. As depicted in Scheme 14, superarmed glycosyl donor **76** proved to be significantly more reactive than its per-benzylated analog **61**; this was reflected in the formation of disaccharide **78** (95%) with only trace amounts of disaccharide **77** present (<5%). In addition, unreacted glycosyl donor **61** was recovered in 87% yield. Furthermore, this concept was found to be universal and applicable to glycosidation of *O*-pentenyl, *S*-ethyl, *S*-phenyl, *S*-tolyl, and *S*-thiazolinyl building blocks [80]. This observed reactivity pattern was also rationalized by the occurrence of the “O-2/O-5 Cooperative Effect” [40].

As described in Fig. 6, stabilization of the glycosyl cation can be achieved either from the lone electron pair on the neighboring endocyclic ring oxygen (O-5) or from the lone electron pair on an acyl type protecting group at O-2, as it is capable of providing stabilization via the formation of the acyloxonium ion intermediate. If both sources of stabilization are available, as in the case of 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl, this combination gives rise to an overall “superarming” protecting group pattern. Alternatively, this type of superarmed glycosyl donor may also be viewed as an armed donor, capable of a 1,2-*trans* stereoselective glycosylation, allowing for the chemoselective introduction of a 1,2-*trans* linkage prior to other linkages.

5 The Involvement of Superdisarmed and Superarmed Building Blocks in Oligosaccharide Synthesis

The expeditious preparation of complex oligosaccharides remains a significant challenge to synthetic organic chemistry. The combined demands of regio- and stereo-selectivity in glycosidic bond formation has led to complex synthetic schemes and extensive protecting group manipulations. As mentioned before, the use of a chemoselective activation strategy avoids such extraneous manipulations, thus offering significant advantages for expeditious glycoside synthesis. Combining the strategic and conceptual updates to the original Fraser-Reid strategy for armed–disarmed oligosaccharide synthesis with the novel concepts for superarming and superdisarming of building blocks has expanded the applicability of chemoselective synthesis to encompass a variety of oligosaccharide sequences. For example, utilization of the cooperative effect allows for the acquisition of *cis*–*cis*-linked oligosaccharides, similar to that discussed previously (see Scheme 7). As shown in Scheme 15, armed STaz glycosyl donor **79** was chemoselectively activated over superdisarmed 3,4-di-*O*-benzoyl-2-*O*-benzyl protected STaz glycosyl acceptor **80** in the presence of Cu(OTf)₂ to give disaccharide **81** in 89% yield [81]. Superdisarmed disaccharide **81** was then glycosidated with standard glycosyl acceptor **14** in the presence of AgOTf to give the desired *cis*–*cis*-linked trisaccharide **82** in 75% yield.

Along similar lines, it was demonstrated that a combination of the *trans*-directing picolyl functionality of armed glycosyl donor **83** and the *cis*-directing functionality of its subsequent

superdisarmed disaccharide **84**, led to a *trans*–*cis* glycosylation pattern, inverse to that of the classic armed–disarmed approach which gives a *cis*–*trans* pattern [81]. The coupling between building blocks **83** and **80** was performed in the presence Cu(OTf)₂/TfOH to give *trans*-linked disaccharide **84** in 70% yield (Scheme 16). The superdisarmed disaccharide **84** was then coupled with glycosyl acceptor **14** in the presence of AgOTf, affording the desired inverse-patterned *trans*–*cis* trisaccharide **85** in 54% yield.

It was also demonstrated that disarmed disaccharide **87** (obtained by classic armed–disarmed approach from building blocks **61** and **86**, Scheme 17) could be further chemoselectively activated over superdisarmed building block **88**. Thus, disarmed disaccharide **87** was activated in the presence of Cu(OTf)₂/TfOH to produce trisaccharide **89** in 70% yield [40].

This concept of conformational superarming was clearly demonstrated by performing a one-pot coupling wherein all three reaction components (thioglycosides **73**, **90**, and **91**) were mixed from the beginning (Scheme 18) [74]. This type of one-pot technique requires differentiation between the reactivity levels of both glycosyl donors (**73** and **90**) and both glycosyl acceptors (**90** and **91**), while all bearing the same anomeric leaving group (phenylthio). The first reaction took place between the superarmed glycosyl donor **73** and the more reactive primary (and also more electron rich due to the neighboring benzyl substituents) glycosyl acceptor **90**. The resulting disaccharide derivative then reacted with the remaining glycosyl acceptor **91**. As a result of this one-pot coupling in the presence of NIS/TfOH, trisaccharide **92** was obtained in 64% yield.

A similar sequence, yet with the execution of the traditional stepwise approach, was explored with the electronically superarmed glycosyl donors. Thus, the superarmed glycosyl donor **93** was activated over “armed” acceptor **94** in the presence of iodine to provide disaccharide **95** in 80% yield (Scheme 19). This disaccharide was then glycosidated with the disarmed acceptor **96** to provide trisaccharide **97** in 55% yield. The resultant trisaccharide was glycosidated with glycosyl acceptor **14** to obtain the target tetrasaccharide **98** in which monosaccharide residues are connected via alternating *trans*–*cis*–*trans* linkages.

In principle, examples of using electronically superarmed building blocks are rather abundant; however, these building blocks were chosen for the convenience of their protecting group pattern rather than in appreciation of the superarmed properties. These examples include the synthesis of HIV viral protein gp120 glycopeptide fragment [82], the synthesis of core tetrasaccharide corresponding to GPI-related mucins of *Trypanosoma cruzi* Y-strain [83], the synthesis of a complex branched oligosaccharide of F1 α antigen 9 [84], etc. [85, 86]. The involvement of superdisarmed glycosyl donors in electrochemical glycosylations was also investigated [87, 88].

6 Conclusions and Outlook

It is critical to make complex carbohydrates more accessible to general chemical, biochemical, and industrial researchers to keep pace with the exploding area of glycobiology. This aim can only be 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 a reasonably efficient route to oligosaccharide assembly have already emerged and the armed–disarmed approach for chemoselective oligosaccharide synthesis is undoubtedly amongst them. Although recent advancements discussed herein have expanded the scope of the armed–disarmed methodology, it is clear that further development of efficient and general methods for the expeditious synthesis of complex carbohydrates will remain an important and active arena for scientific endeavors during the twenty-first century.

Other remarkable improvements in oligosaccharide synthesis have also emerged, including one-pot protection [89] and glycosylation strategies [50, 51, 90], polymer-supported [91–93] and automated synthesis [94, 95], fluorous tag assisted synthesis in microreactors [96], and surface-tethered iterative carbohydrate synthesis (STICS) [97]. The chemoselective strategy, however, is still occupying an important niche in the arsenal of available methods. In the coming years, glycoscientists are expected to have developed simple, efficient, and flexible approaches to oligosaccharide assembly that will complement existing methodologies and bring our ability to obtain complex oligosaccharides up to a significantly higher level.

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Abbreviations

1,2-DCE	1,2-Dichloroethane
Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
Cbz	Benzyloxycarbonyl
CDA	Cyclohexane 1,2-diacetal
DMTST	Dimethyl(thiomethyl)sulfonium trifluoromethanesulfonate (triflate)
Et	Ethyl
IDCP	Iodonium(di- δ -collidine)perchlorate
LG	Leaving group
NIS	<i>N</i> -Iodosuccinimide
PFBz	Pentafluorobenzoyl
Ph	Phenyl
Phth	Phthalimido
Pic	Picolinyl
RRV	Relative reactivity value
SBox	<i>S</i> -Benzoxazolyl
STaz	<i>S</i> -Thiazoliny
TBDMS	<i>tert</i> -Butyldimethylsilyl (also TBS)
TBSOTf	<i>tert</i> -Butyldimethylsilyl trifluoromethanesulfonate (triflate)
TESOTf	Triethylsilyl trifluoromethanesulfonate (triflate)
TfOH	Trifluoromethanesulfonic acid
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate (triflate)

Tol Toly

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Fig. 1.
Representative examples of natural poly- and oligosaccharide sequences

Fig. 2.
The disarming effects of the cyclic ketal/acetal are both conformational and electronic

Fig. 3.
Effect of axial and equatorial electron-withdrawing substituents on basicity of piperidines

Fig. 4.
O-2/O-5 Cooperative effect in glycosidation of the superdisarmed building blocks

Fig. 5.

Basicity and reactivity increase with the increase of the number of axial hydroxyls:
conformational change to increase reactivity

Fig. 6.
O-2/O-5 Cooperative effect in glycosidation of the superarmed building blocks

Scheme 1.
Outline of chemical glycosylation

Scheme 2.
Conventional (linear) oligosaccharide synthesis

Scheme 3.
Armed-disarmed strategy outline

Scheme 4.

Armed (**1**) and disarmed (**2**) *O*-pentenyl glycosides: synthesis of *cis-trans*-patterned trisaccharide **5**

Scheme 5.

Synthesis of *cis-cis*-patterned trisaccharide **10**, via the modified armed-disarmed approach [34]

Scheme 6.

Arming participating picolinyl group mediated synthesis of *trans-trans*-patterned trisaccharide **15**

Scheme 7.

Disarming the glycosyl acceptor with the remote 6-*O*-pentafluorobenzoyl moiety: direct synthesis of *cis-cis*-patterned trisaccharide **20**[44]

Scheme 8.

The disarming of building blocks can be achieved with a benzylidene acetal or isopropylidene ketal [48]

Scheme 9.

One-pot synthesis of trisaccharide **29** via torsional deactivation with cyclohexane 1,2-diacetal (CDA)

Numbers represent ratio
of products in the
competition reactions

The reactivity of a series of partially benzoylated rhamnosides falls between the traditional armed (**25**) and disarmed (**41**) building blocks

Scheme 11.

Relative reactivity levels of differently protected galactosides. Synthesis of tetrasaccharide **54** via the programmable one-pot strategy [47]

Scheme 12.

Chemoselective activation of disarmed donors **55** or **58** over superdisarmed acceptors **56** or **59**, respectively

Scheme 13.

Chemoselective activation of the conformationally superarmed glycosyl donor **73** over armed glycosyl acceptor **74**

Scheme 14.

Superarmed (**76**) and armed (**61**) glycosyl donors in competitive glycosylation

Scheme 15.

Sequential activation of armed $\rightarrow$ superdisarmed building blocks for direct synthesis of *cis-cis*-linked oligosaccharide **82**

Scheme 16.

Sequential activation of picolyated armed $\rightarrow$ superdisarmed building blocks: synthesis of *trans-cis*-linked trisaccharide **85**

Scheme 17.

Sequential activation of armed $\rightarrow$ disarmed $\rightarrow$ superdisarmed building blocks **61**, **86**, **88**, respectively [40]

Scheme 18.

Superarmed → armed → disarmed activation for the synthesis of trisaccharide **92** in one-pot

Scheme 19.

Synthesis of tetrasaccharide **98** using superarmed $\rightarrow$ armed $\rightarrow$ disarmed sequential activations [80]

Table 1Comparative activation of differently protected SBox glycosides **58**, **61**, and **62**

Entry	Donor	Product	Yield	α/β ratio
1	<p>61</p>	64	89%	5.4/1
2	<p>58</p>	65	70%	β only
3	<p>62</p>	66	No reaction	—

Table 2

Comparative glycosidations of glycosyl donors **58**, **61**, and **76**

Entry	Donor	Time	Product	Yield	α/β ratio
1		2 h	77	91%	1.2/1
2		16 h	–	No reaction	–
3		< 5 min	78	90%	β only