Reciprocal Donor Acceptor Selectivity (RDAS) and Paulsen's Concept of "Match" in Saccharide Coupling

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Dedicated to Professor Hans Paulsen

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Three modes of selectivity — enantio, stereo, and regio — are critically important for efficient organic synthesis. In the sub-domain of oligosaccharide synthesis, the first is (usually!) irrelevant in view of the chiralities of the reacting partners. The challenge posed by the other two is compounded by the reality that "protecting groups" are the major, if not only, instruments by which control can be exercised. The role that O2 protecting groups play in stereocontrol of coupling reactions was formulated 60 years ago. In this microreview, evidence is presented which shows that O2 protecting groups also exercise regiocontrol.

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Introduction

In his seminal 1982 review entitled "*Advances in Selective Chemical Syntheses of Complex Oligosaccharides*" Paulsen, the quintessential practitioner of the craft, issued the following cryptic observation: "*Although we have now learned to synthesize oligosaccharides, it should be emphasized that*

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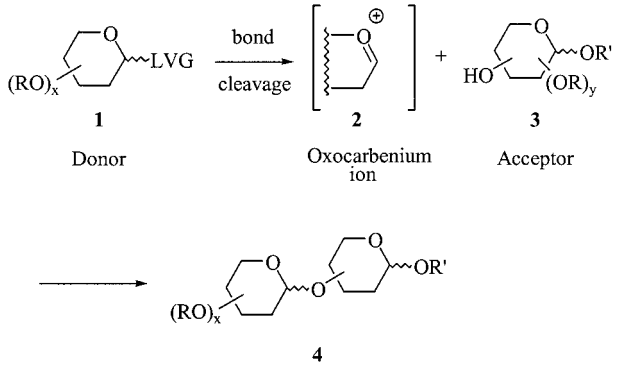
MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

each oligosaccharide synthesis remains an independent problem, whose resolution requires considerable systematic research and a good deal of know-how. ***There are no universal reaction conditions for oligosaccharide syntheses***'' (emphasis added).[1] The implication of this warning, as Paulsen clarified subsequently, is that donors and acceptors must be ''matched'' for best results.[2] The insight which led to this pronouncement was distilled from years of collective experience in the minefield of carbohydrate synthesis. However, the data bank of successes and failures did not provide guidelines for determining how the best match of partners could be revealed. Nevertheless, it was clearly implied that a good coupling should go-with-the-flow and, by corollary, ''forcing conditions'' should not be required. One option was to carry out several preliminary trial-and-error experiments, and a well-rewarded example of such a heroic approach is the elegant synthesis of a heparin construct by van Boeckel and Petitou.[3]

Paulsen's caveat gains contemporary relevance in light of recent reports on automated,[4−6] one-pot,[7] and programmed[8] oligosaccharide synthesis.

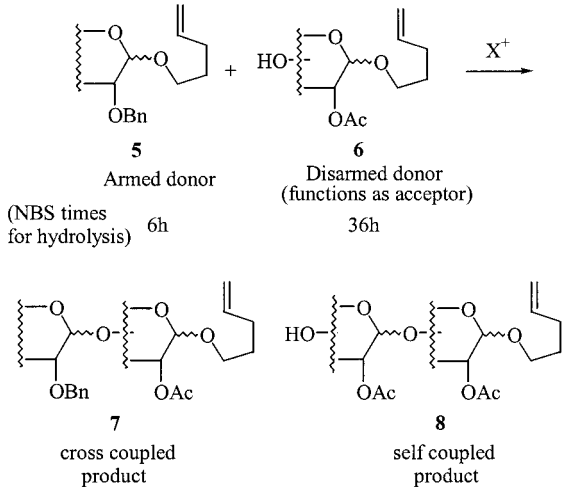
Background

The process depicted in Scheme 1 should be simple to execute! Placement of a good leaving group on one partner, **1**, and a free OH on the other, **3**, should result in ready coupling to give **4**, in keeping with the tenets of nucleophilic substitution. However, Pictet's 1928 foray into sucrose synthesis[9] demonstrated the perils of such a callow analysis. Greater sophistication was needed, and the emergence of Isbell's seminal[10] 1940 concept of neighboring group participation,[11] not only codified the requirements for 1,2-*trans* glycosidation, but helped to usher in the grand age of physical organic chemistry.[12] Lemieux's fifty-year old analysis of ''*Replacement reactions at the anomeric center*'' lay much of the foundation upon which today's successes still rely.[13]



Scheme 1. Glycosylation of donor **1**, and acceptor **3**

As is apparent from Scheme 1, protecting groups are a necessary evil in oligosaccharide synthesis,[14] and so making creative use of them has been of primary interest in this group, beginning with the 1988 description of the armed/disarmed concept for glycoside coupling.[15] In this exercise, strategic placing of acyl and alkyl protecting groups on two *n*-pentenyl glycosides (NPGs) was used to direct the outcome of the coupling, as illustrated in Scheme 2. The chemoselectivity evident in the process relies ultimately on the relative reactivity[16] of the two NPGs. The fact that acylated donors are less reactive than their alkylated counterparts had been recognized earlier by Paulsen and co-workers.[17]



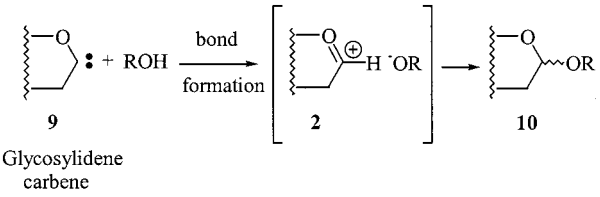
Scheme 2. Armed/disarmed saccharide coupling

The result in Scheme 2 showed that these reactivity differences could be exploited for synthetic advantage. Thus, the simple difference in O2 protecting groups in **5** and **6** was enough to consign (the otherwise excellent) donor **6** to the role of an acceptor towards **5**. Notably, the self-coupled product, **8**, was not obtained — a detail which will be rationalized later in this article. Subsequently, the constraint imposed by cyclic acetals, for example a 4,6-*O*-benzylidene ring, was shown to cause ''torsional disarmed'' effects[18] which complement the ''electronic disarmed'' effects depicted in Scheme 2.

The rapid acceptance of the armed/disarmed strategies[19,20] into the fabric of carbohydrate chemistry paved the way for significant developments in reactivity manipulation of glycosyl donors, both on the glycon as well as the aglycon. For example with the latter, hindered alkyl thioglycosides[21] were tested, as were variously activated phenyl thioglycosides.[22,23] Ley and co-workers combined torsional and electronic armed/disarmed effects for ''reactivity tuning'' of donors.[24] Other donor refinements include semi-disarmed,[25] latent/active,[26] orthogonal,[27] and, most recently, semi-orthogonal.[28]

A novel and ingenious strategy for glycosidation, conceptually different from that depicted in Scheme 1, was devised by Vasella.[29] The new type of donor was a glycosylidene carbene, **9**, (Scheme 3) a reactive molecule generated in situ, which abstracts a proton from an alcohol to form the ox-

ocarbenium ion **2**, thereby simultaneously generating an alkoxy partner. The ion pair then collapses to the glycoside **10**.



Scheme 3. Vasella's glycosylidene carbene strategy for glycosidation

Comparison of Schemes 1 and 3 shows that glycosylidene carbenes rely on bond formation to a proton, to generate the oxocarbenium intermediate, **2**, whereas "classical donors" rely on bond cleavage of the leaving group (LVG) to achieve the same objective. The most able proton donor is therefore the site of interest (Scheme 3) and the fact that this propensity can be assessed by H-bonding analysis of the substrate is a tremendous advantage.[30]

Noteworthy features of Vasella's chemistry are the shift in focus (*a*) from the donor, the perennially preferred partner, to the acceptor, and (*b*) from the nucleophilicity of the OH in question, to its acidity.

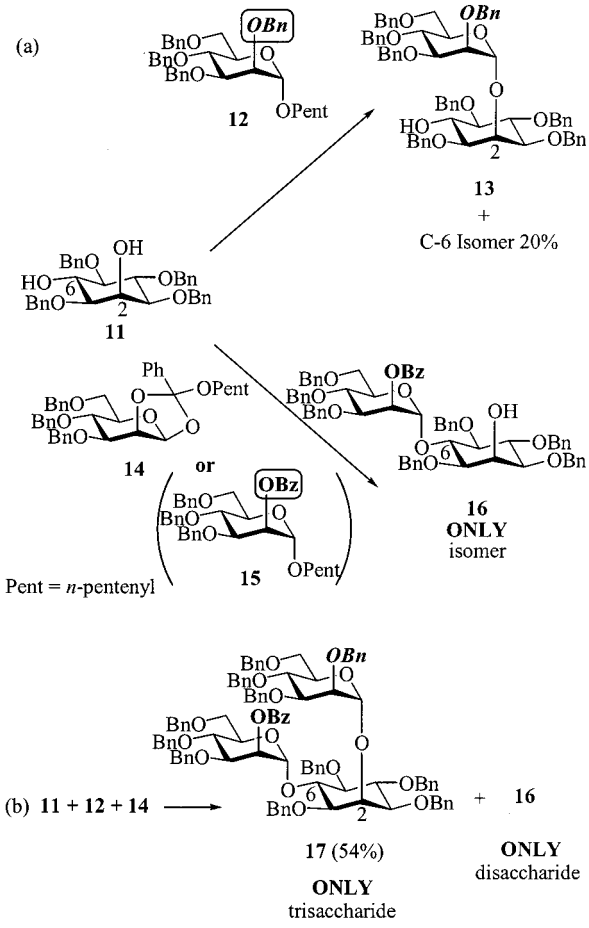
A Serendipitous Observation

The impetus to revisit Paulsen's concept of "match" in glycosidation reactions emanated from the serendipitous observations summarized in Scheme 4 (a). We had found that the inositol diol **11** reacted with the tetra-*O*-benzyl NPG **12** mainly at C2-OH to give **13**, while the NPOE **14** reacted *exclusively* at C6-OH to give **16**.[31] Even more fascinating was the three-component reaction between acceptor **11** and donors **12** and **14** (Scheme 4, b), which produced a single trisaccharide **17** in 54% yield (unoptimized), each donor having gone to its preferred OH based on the two-component tests in Scheme 4 (a).[31]

Were these selectivities tied to the NPOE (**14**) that had been used? These unique donors are confined to the *n*-pentenyl family. (Thio-orthoesters are known, but their use as donors has not met with success).[32] 2-*O*-Acyl *n*-pentenyl glycoside (NPG_{AC}) counterparts, such as **15**, are disarmed and therefore less reactive than the corresponding NPOE (**14**). However, as indicated in Scheme 4 (a), donor **15** displayed the same total regioselectivity for the C6-OH of **11**.

Reciprocal Donor Acceptor Selectivity (RDAS)

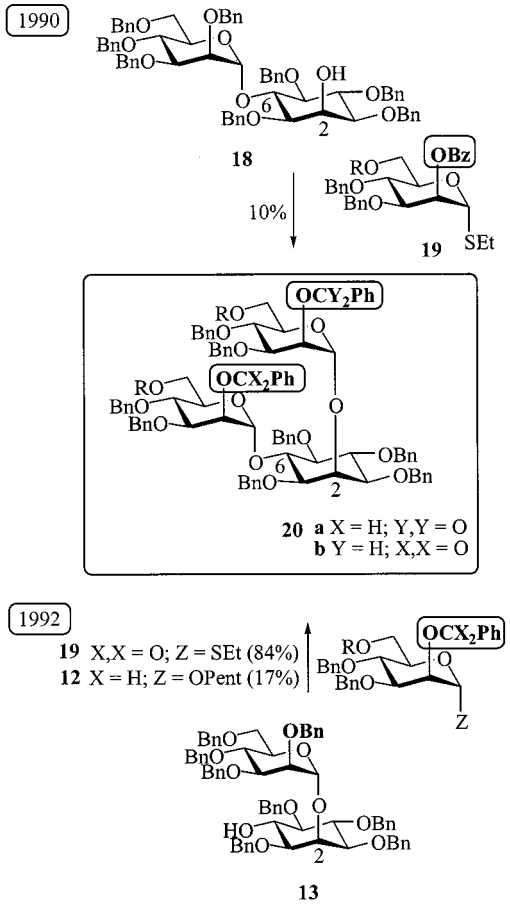
The two-component reactions in Scheme 4 (a) implied that each OH of the diol exhibited a preference for one of the donors, and vice versa! This Reciprocal Donor Acceptor Selectivity (RDAS)[33] was manifested in the three-component reaction in Scheme 4 (b) that produced a single trisaccharide **17** out of four possibilities, and equally remarkably a single disaccharide **16**. Notably, both products of the three-component-reaction, **17** and **16**, result from the RDAS preferences observed in Scheme 4 (a). The regioselectivity seemed to be tied to the *O*2 protecting group of the donor **12** versus **14**/**15**, (i.e. benzyl versus benzoyl) respectively.



Scheme 4. Serendipitous observations of some glycosylations

Supporting evidence for this selectivity is difficult to find in the literature, because synthetic projects utilize a wide palette of "forcing conditions" to ensure the desired outcome. Such experiments would not be enlightening, since they would not reveal the go-with-the-flow "match" proposed by Paulsen and evident in the RDAS-controlled processes that had led to **17** and **16** *only*. Furthermore, couplings that proceed in unflattering yields, i.e. non-*RDAS* relationships, are usually not reported.

Fortunately, a telling example was found in published work by van Boom and co-workers (Scheme 5). Their 1990 attempt to prepare the pseudotrisaccharide **20a** was deemed unsatisfactory because only a 10% yield had been obtained from reaction of pseudodisaccharide **18** with the 2-*O*-benzoyl thioglycoside **19**.[34] In a change of strategy two years later, pseudodisaccharide **13** was found to react with the same donor **19** to give the analogous pseudotrisaccharide **20b** in 84% yield (Scheme 5).[35]



Scheme 5. Evidence in support of RDAS....Part 1

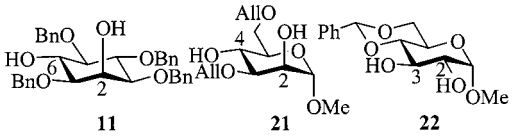
The message from the preceding paragraph seemed to be that the order for installing the mannoses of **20** should be *O*2 before *O*6; however, an attempt in our laboratory to replicate van Boom's 1992 work using the 2-*O*-benzyl NPG **12** proceeded in only 17% yield.[36] The message from van Boom's 84% and our 17% yield is that the 2-*O*-benzoyl donor, **19**, "matches" the C6-OH, while the 2-*O*-benzyl analog, **12**, does not — a conclusion that coincides with our serendipitous two-component observations outlined in Scheme 4 (a).

What About Some Other Diols?

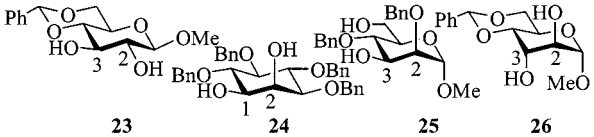
Further analysis of the regioselective preferences of donors required uniform conditions, and so for exploratory studies *n*-pentenyl donors [orthoester (NPOE)/2-*O*-acyl (disarmed) NPG_{AC} and 2-*O*-alkyl (armed) NPG_{ALK}] were used under similar experimental conditions. In addition, *manno* donors were chosen because α-selective coupling could be taken for granted as the major reaction pathway owing to the pronounced kinetic anomeric effect of mannose.[37] Product analysis would therefore be simplified.[38]

Two component reactions of the diols with *n*-pentenyl donors were tested (Table 1).[33,39] With the notable exception of the β-glucoside **23**, NPOE/NPG_{AC} donors were *always* overwhelmingly, if not completely, regioselective. By contrast, the NPG_{ALK} was *always* promiscuous, showing mediocre selectivity.

Table 1. Observed regioselectivity in two-component glycosylation reactions of *n*-pentenyl donors with some diols



Donor	*O*-6 *O*-2	*O*-4 *O*-2	*O*-3 *O*-2
NPOE/NPG_{AC}	ONLY -	ONLY -	1 : 7.6
NPG_{Alk}	1 : 3	- ONLY	3 : 1

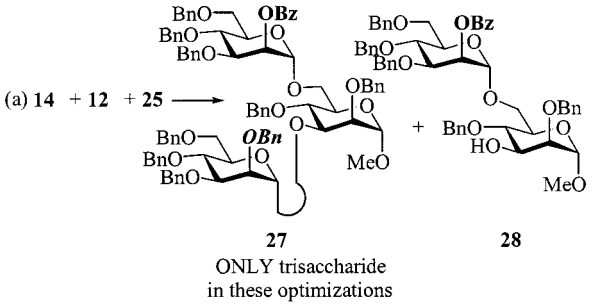


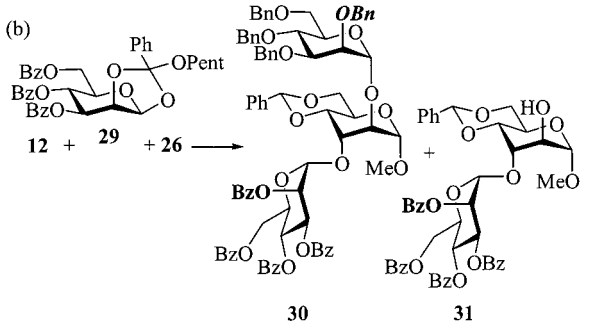
Donor	*O*-3 *O*-2	*O*-1 *O*-2	*O*-6 *O*-3	O-3 *O*-2
NPOE/NPG_{AC}	1 : 3.5	6 : 1	ONLY -	ONLY -
NPG_{Alk}	2.9 : 1	2 : 1	2 : 1	3 : 1

The Question of Steric Hindrance

Steric hindrance could conceivably "explain" the preference in diols **11**, **21** and **24**, the equatorial OHs being less hindered than the axial OHs. Steric hindrance could also "explain" the preference for the primary OH in **25**. However, the result for diol **26** points to something less prosaic. Thus, although the OHs of altroside **26** offer unambiguous steric options, the more hindered C3-OH reacts exclusively with the NPOE/NPG_{AC}.

Diols **25** and **26** were chosen for closer examination (Scheme 6) because each offers clear steric preferences. The two-component data summarized in Table 1 indicate that donors, whether armed or disarmed, prefer the same OH, namely C6-OH in **25** and C3-OH in **26**.[33,39] In view of the fact that both donors exhibit the *same* regioselective preference, it was of interest to see how the three-component, double-differential glycosidation would play out in these cases. The contrast with the example in Scheme 4 (a) should be noted, for in that case each donor had clearly preferred a different OH of diol **11**, and in the three-component reaction (Scheme 4, b) each donor had exhibited that preference.





entry	29	26	12	30	31
i	1 equiv	1 equiv	1 equiv	27%	45%
ii	1 equiv	1 equiv	1.3 equiv	37%	37%
iii	1 equiv	1 equiv	1.6 equiv	43%	31%
iv	1 equiv	1 equiv	2 equiv	52%	19%
v	1 equiv	1 equiv	3 equiv	57%	16%

Scheme 6. Three component double differential glycosidation controlled by RDAS

In the event, it is seen that *the two-component preferences in Table* 1 *notwithstanding*, when both donors were made to *compete* in Scheme 6, the only trisaccharide *and* disaccharide obtained, **27** and **28**, resulting from the disarmed NPG_{AC} **15**, reacting at C6-OH. Strikingly absent were tri- and disaccharides from reaction of the armed donor with the primary OH of **25**.

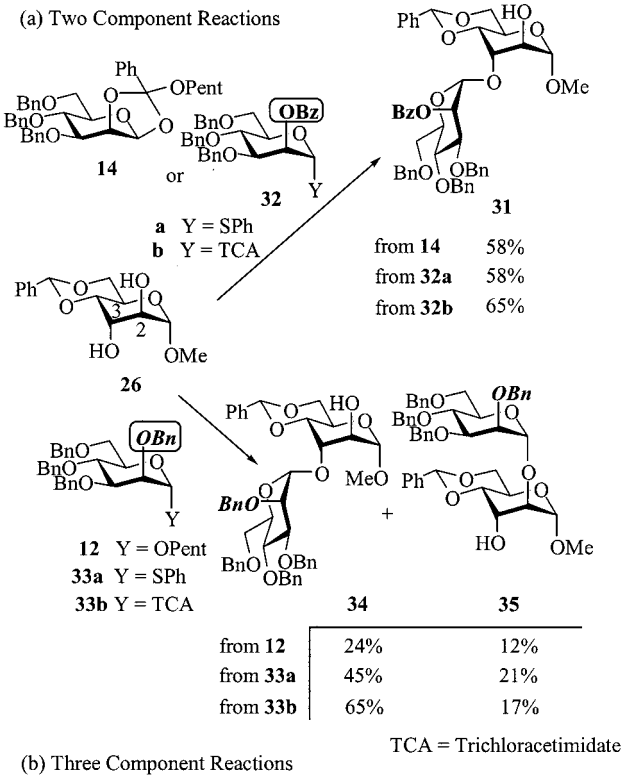
For diol **26**, the data from the two-component reactions (Table 1) show higher selectivities for both NPOE and NPG_{ALK} donors for the C3-OH. Again, although both donors prefer the C3-OH, the three-component competition produced tri- and disaccharides, **30** and **31** (Scheme 6, b, entry *i*), in accordance with RDAS preferences of NPOE **29**.

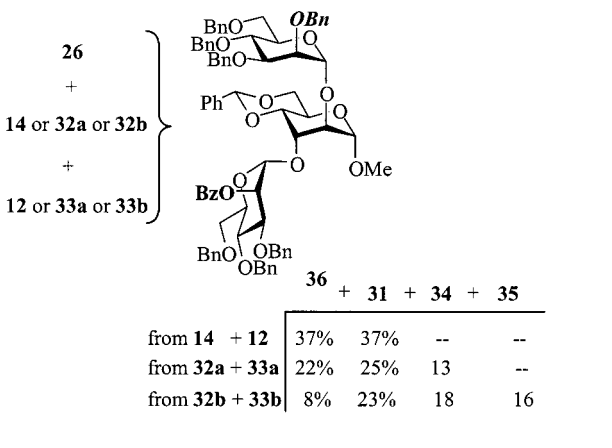
Had disaccharide **31** reacted with the armed donor **12**, the yield of trisaccharide **30** would have been higher. Could higher yields be induced by increasing the molar ratio of the armed donor **12**? The answer in Scheme 6 (b, entries *ii* − *v*) is affirmative, with a steady increase in the yield of trisaccharide **30**. Thus, even with the audacious excess of armed donor **12** (3 equiv.) entry (*v*), NPOE **29** won the competition resulting in 57% yield of trisaccharide **30**, with concomitant diminution of disaccharide **31** from 45 to 16%.[40]

The results in Schemes 6a and 6b suggest that the NPG_{AC}/NPOE are "matched" with the C6-OH of **25**, and C3-OH of **26**, and hence the preference of these donors is expressed in spite of the generous excess of the competing armed donor.

What About Thioglycosides and Trichloroacetimidates?

It was clearly necessary to determine whether these regioselectivities were confined to the *n*-pentenyl family. Thioglycosides and glycosyl trichloroacetimidates are the most widely used glycosyl donors, and so they were obvious choices for comparisons. Thus, the disarmed thioglycoside





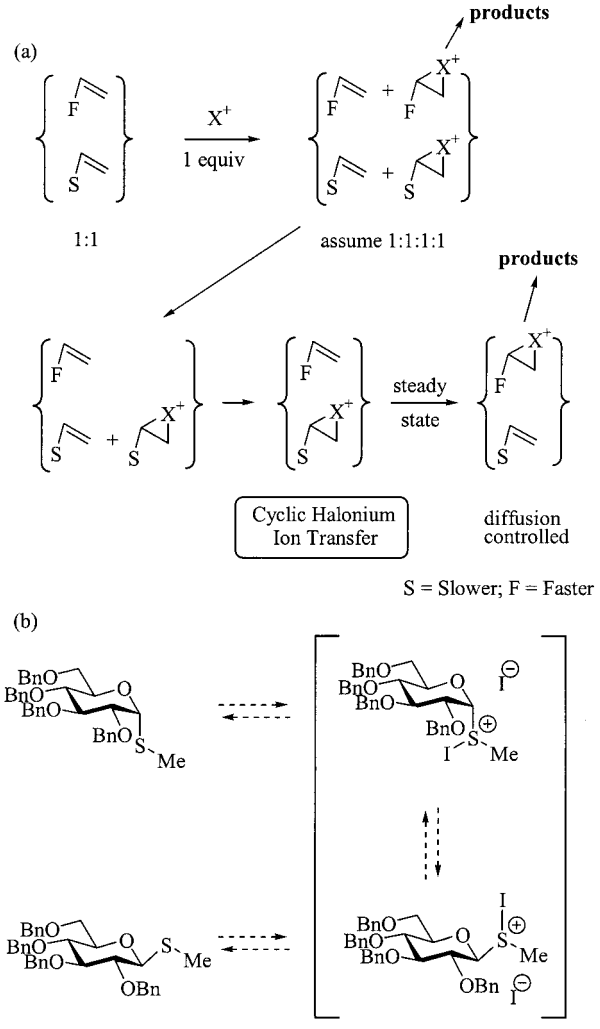
Scheme 7. Trichloacetimidate and thioglycoside donors

and trichloroacetimidate, **32a** and **32b**, respectively, were compared with NPOE **14**. [Recall from Scheme 4 (a) that NPOE and NPG_{AC} counterparts (e.g. **14** and **15**) exhibit the same regioselectivity, even though yields and rates may differ.][41]

The diol **26** was chosen as the test substrate. The data in Scheme 7 show the same exclusive reaction at the C3-OH for the NPOE/disarmed donors, **32a,b** and **14** giving disaccharide **31** in comparable yields. Similarly, the armed counterparts **33a**,**b** and **12** are promiscuous in all cases, reacting with both of the hydroxyl groups, although primarily with C3-OH, to give **34** and **35**. The agreement in regioselectivities as well as yields is remarkably good for all three donors.[42]

However, the three-component reactions show interesting differences. Thus, with all three donors: (*1*) compound **36** is the only trisaccharide (of four possibilities) that is formed; and (*2*) the major disaccharide, **31**, arises from the NPOE/disarmed donors reacting at C3-OH.

We therefore conclude that there is a "match" between the C3-OH and NPOEs as well as 2-*O*-benzoyl donors *of any type*. However, the low yield (8%) of trisaccharide **36** with the trichloroacetimidate requires comment.



Scheme 8. Intermolecular halonium ion transfer

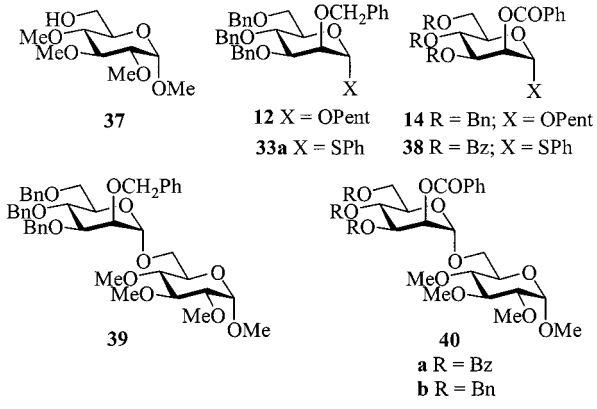
Reactions with trichloroacetimidates had to be done at −78° to avoid migration of the acceptor's benzylidene ring to C3/C4. The simplest rationalization, therefore, is to assume that at −78 °C the disarmed donor, **32b**, reacts so sluggishly that competition favors the armed counterpart **33b** leading to **34** and **35**. However, we suggest that there is another factor at work, namely intermolecular halonium-ion transfer.

Intermolecular Halonium-Ion Transfer

The elegant work of Brown and co-workers[43] on the early steps of electrophilic bromination identified intermolecular cyclic brominium ion transfer as a hitherto unrecognized process in "sterically encumbered olefins". However, recent work in our laboratory has shown that the process is general. Thus, as illustrated in Scheme 8 (a), if two unhindered alkenes are made to compete for one equivalent of halonium ion, X^+, a steady-state regime can be envisaged whereby the faster reacts completely, and the slower is recovered completely. Indeed, our work showed that this is possible even when the relative reactivity of the olefins is as small as 2.6.[44]

Thioglycosides are known to undergo α→β anomerization upon activation with iodonium ion. Boons[45] and Field[46] have rationalized this equilibration by invoking in-

Table 2. Intermolecular halonium ion transfer



Entry	Type	Donors Armed/Disarmed (1 equiv each)		NIS	Product Ratio 39 ------ 40a/b
(i)	Thio vs Thio	**33a**	**38**	1 equiv	1 --------- 0
(ii)	Thio vs Thio	**33a**	**38**	3 equiv	1 ------- 1.6
(iii)	NPG vs NPG	**12**	**14**	1 equiv	2 --------- 1
(iv)	NPG vs NPG	**12**	**14**	3 equiv	1.1 --------- 1
(v)	NPG vs Thio	**12**	**38**	1 equiv	1 --------- 0
(vi)	NPG vs Thio	**12**	**38**	3 equiv	1 ------- 2.2

termolecular iodonium ion transfer, as summarized in Scheme 8 (b).

We have tested for the intervention of intermolecular halonium ion transfer, as shown in Table 2.[47] Equimolar mixtures of acceptor **37** and various armed and disarmed donors were allowed to compete for NIS. For the thioglycosides **33a** and **38**, use of one equivalent of NIS, entry (*i*), led to product **39** by reaction of the armed donor **33a**, as was to be expected. However, with three equivalents, entry (*ii*), the *major* product was from reaction with the disarmed donor **38**.

Similar tests with the armed and disarmed NPGs **12** and **14**, respectively, gave similar, although less dramatic, results (entry *iii*). Notably, with three equivalents of promoter (entry *iv*), the ratio of the disarmed product **40b** increased substantially. That the exchange can occur between thioglycosides and NPGs is clear from entries (*v*) and (*vi*). Thus, when the armed NPG **12** and disarmed thioglycoside **38** were presented with one equivalent of promoter, only the armed NPG reacted to give **39**. However, when the amount of promoter was increased to three equivalents, the major product **42a** (57%) came from the disarmed thioglycoside **38**.

The results in entries (*i*), (*iii*) and (*v*) indicate agreement with the rationalization depicted in Scheme 8 (a).[37] Thus, the armed donor consumes all of the promoter, which is not surprising. However, in entries (*ii*), (*iv*) and (*vi*), there is enough promoter to activate both armed and disarmed donors simultaneously and hence the steady-state competition that drives iodonium transfer in Scheme 8 (a) no longer controls the outcome. Each of the two donors can therefore express its preference. The result is that the 2-*O*-benzoyl/disarmed donors are better "matched" with the acceptor — when the playing field is level.[47]

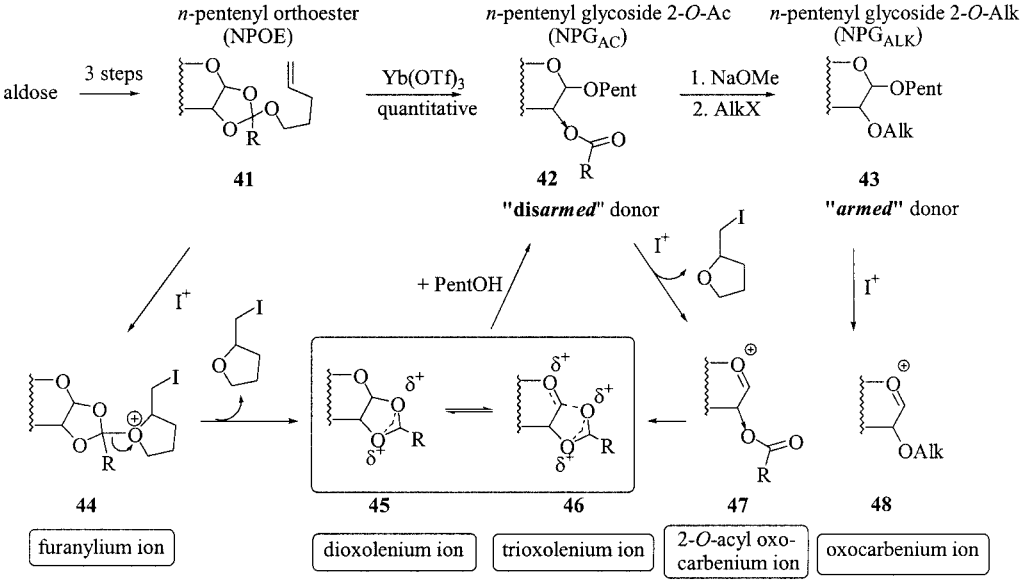
Reactivity Issues

Although the serendipitous observations (Scheme 4) and early studies were carried out with *n*-pentenyl donors, it is clear from the results in Scheme 7 (a) and Table 2 that the RDAS principle may apply to other types of donors.

In order to initiate an inquiry into the basis for the selectivities evidenced above, theoretical studies have been undertaken with the help of Grimme and Piacenza.[48] Donors **41**, **42** and **43** (Scheme 9) were modeled by the tetrahydropyrans **49**, **50** and **51**, respectively, and the intermediates **44**−**48** by cations **52**−**55**. The values obtained from MP2 and DFT calculations are represented in Figure 1.

In an attempt to correlate the chemoselectivities in Scheme 4 with the reactivities of the donors, we made use of our 1995 protocol for determining the relative reactivity of glycosyl donors.[49] This analysis showed that the general order for donor reactivity was NPOE >>> NPG_{ALK} > NPG_{AC}. However, the results in Scheme 4 showed that the most- and least-reactive donors, NPOE **14** and NPG_{AC} **15**, respectively, displayed the same exclusive selectivity for the C6-OH of **11**, while the donor of "middle" reactivity, NPG_{ALK} **12**, was promiscuous. *In short, there was no apparent correlation between reactivity and selectivity.*

Figure 1 provides a rationale for the agreement between the most- and least-reactive donors. Thus, the NPOE model **49** goes directly to the attractive di/trioxolenium complex



Scheme 9. The family of *n*-pentenyl donors

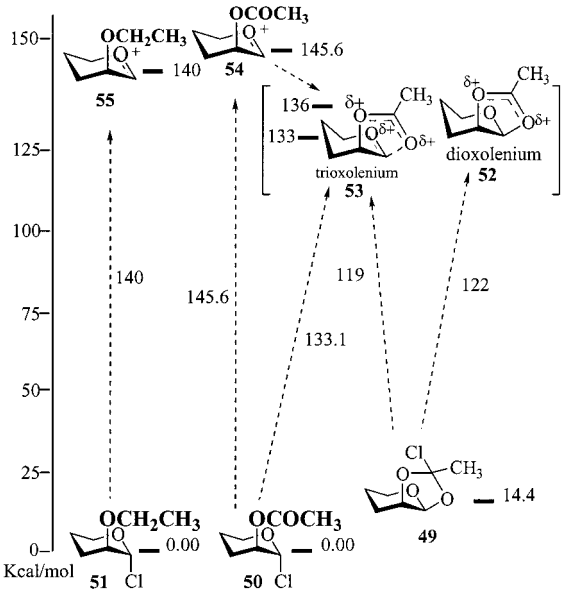


Figure 1. Observed regioselectivity in two-component glycosylation reactions of *n*-pentenyl donors with some diols

52/53.[48] This complex is also available to the 2-*O*-acyl donor, **50**, directly by 133.1 kcal/mol, or indirectly via the oxocarbenium ion **54** at much higher cost (145.6 kcal/mol). Intuitively, donor **50** should choose the less energetic pathway by going directly to **52/53** by synchronizing chloride departure with acetyl neighboring-group participation. However, this synchronization usually does not take place otherwise disarmed donors would always react faster than armed, and there would be no armed/disarmed competition such as seen in Table 2 entries *i*, *iii* and *v*.[50]

Summary

The evidence presented above shows clearly that regioselective glycosidation of diols can be controlled by the donor's O2 protecting group, and that this selectivity can be exploited for double differential glycosidations of diols. The usually exclusive *regio*selectivity of O2 benzoyl groups in contrast to the promiscuity of benzyl analogues cannot be assigned to steric hindrance or simple reactivity considerations. The competition experiments in Table 2, where a single OH is made to compete for armed and disarmed donors in the presence of one or three equivalents of NIS (a) indicate the controlling effect of intermolecular halonium ion transfer in reactions of *n*-pentenyl donors and thioglycosides, (b) suggest that in three component reactions, when halonium ion transfer is not at work, a switch in reactivity between armed and disarmed donors takes place by use of either one or three equivalents of NIS, and (c) support the existence of "match" between donor and acceptor as proposed originally by Paulsen.

The energy data in Figure 1 support the armed/disarmed phenomenon, but also reveal that disarmed donors do not always take the less energetic pathway! An "explanation" for this counterintuitive finding awaits further study.

Thus far, RDAS studies have focused heavily on the donor since the "other" partner in Scheme 1 is traditionally ignored. However, "explanations" for the acceptors' selectivities are clearly needed to fully understand the choices shown in Table 1. Hopefully, tinkering with the acceptor will be as informative as tinkering with the donor has been.

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[50] Interestingly, the calculations[48] show that in the case of *gluco* derivatives there is no energy distinction between di- and trioxolenium ions as there is in their *manno* counterparts.

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