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Indolylthio glycosides as effective building blocks for chemical glycosylation

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ABSTRACT: *S*-Indolyl (SIn) anomeric moiety was investigated as a new leaving group that can be activated for chemical glycosylation under a variety of conditions including thiophilic and metal-assisted pathways. Understanding of the reaction pathways for the SIn moiety activation was achieved via the extended mechanistic study. Also reported is how the new SIn donors fit into selective activation strategies for oligosaccharide synthesis.

Introduction

Chemical synthesis of glycan sequences of even moderate complexity still remains a considerable challenge. As such, the development of efficient strategies for the oligosaccharide

and glycoconjugate synthesis has been a demanding area of research effort worldwide. A vast majority of glycan syntheses is nowadays accomplished using thioglycosides¹⁻⁴ and Otrichloroacetimidates (TCAI).⁵⁻⁷ As a part of the ongoing research effort in our laboratory to develop versatile methods for chemical glycosylation and expeditious oligosaccharide synthesis, we became interested in glycosyl thioimidates, glycosyl donors equipped with SCR₁=NR₂ leaving group.⁸ Among a variety of thioimidates studied by us and others, S-benzoxazolyl (SBox),⁹ S-thiazolinyl (STaz),¹⁰ and S-benzimidazolyl (SBiz)¹¹ moieties were found to be excellent building blocks for oligosaccharide synthesis. We also determined that thioimidates fit into practically all existing expeditious strategies for oligosaccharide synthesis due to the unique reaction conditions associated with their activation.¹² In addition, the glycosyl thioimidates led us to the development of conceptually new strategies for oligosaccharide synthesis: the inverse armed-disarmed strategy, temporary deactivation concept, O-2/O-5 cooperative effect, coordination-assisted glycosylation, and Surface-Tethered Iterative Carbohydrate Synthesis (STICS).¹² At the core of the study presented herein is the development of a new method for chemical glycosylation and expeditious oligosaccharide synthesis based on (1H-indol-2-yl)thio (S-indolyl, SIn) glycosides. These compounds are similar to thioimidates developed previously, but the study reported herein unexpectedly revealed that SIn glycosyl donors act neither as thioimidates nor as conventional alkyl/aryl thioglycosides in glycosylation.

Results and Discussion

The thioindole (HSIn) aglycone was obtained from commercially available oxindole (2indolone) by means of thionation with P_2S_5 in tetrahydrofuran (THF).¹³ HSIn was then reacted with a variety of bromide precursors in the presence of potassium carbonate and 18-crown-6 to afford the respective SIn glycosides. Thus, as depicted in Scheme 1, per-benzylated glucosyl bromide 1^{14} was converted into SIn glycoside 2 in 63% yield. Per-benzylated glucosyl 3 and galactosyl bromide 5, freshly prepared from the corresponding ethyl thioglycosides,¹⁵⁻¹⁸ were converted into SIn glycosides 4 and 6 in 60 and 52% yield, respectively. We acknowledge that these yields are far from excellent, but would like to note that the yields listed herein are after crystallization. For X-ray structure determination of glucose derivative 2 and galactose derivative 6, crystals of appropriate dimensions were obtained by slow evaporation of ethyl acetate/hexane solutions. Refer to the experimental section and the SI for complete details of X-ray structure determination of compounds 2 and 6.





With novel SIn glycosides **2**, **4** and **6** in hand, we endeavored for investigation of their properties as glycosyl donors. To study the preliminary scope of this approach, we chose model glycosyl acceptors $7-10^{19}$ depicted in Figure 1. As possible activators, we decided to rely on the reaction

conditions that worked well with thioimidates (AgOTf or AgBF₄), and thioglycosides (NIS/TfOH). To our great surprise, no activation took place when we attempted to react SIn donor **2** with reactive primary acceptor **7** in the presence of AgOTf at rt. Even large excess of 3.0 equiv and prolonged reaction time (24 h) produced no desired disaccharide **11**²⁰ (Table 1, entry 1). For comparison, the SBox LG could be smoothly and rapidly activated with 2.0 equiv of AgOTf.⁹





A drastic change was noted when $AgBF_4$, another effective activator for thioimidates,²¹ was employed as the promoter for SIn donor **2**. Although this reaction required 5.0 equiv of $AgBF_4$, it could be smoothly driven to a completion in 5 h. As a result, disaccharide **11** was produced in a good yield of 85% (entry 2). In our prior experience, silver triflate and tetrafluoroborate act similarly,²¹ and to explain this discrepancy in application to the SIn glycosides we came up with the following hypothesis. We thought that this could be due to SIn glycosides being particularly sensitive to the marginal difference in the availability of Ag^+ ions between these two promoters. Therefore, we looked at alternative sources of silver, and silver salt/Lewis acid cooperative promoter system recently developed by us for the activation of bromides²² and chlorides²³ appealed to us as a possible solution. However, when donor **2** was coupled with standard acceptor **7** in the presence of Ag_2CO_3 (1.0 equiv) and TMSOTf (2.0 equiv) disaccharide **11** was produced only in a poor yield of 20% in 19 h (entry 3). The reaction was significantly

accelerated in the presence of Ag_2CO_3 and a larger excess of TMSOTf (4.0 equiv), and disaccharide **11** was obtained in 87% yield in 2 h (entry 4). Being generally encouraged by this outcome, albeit realizing that large excess of TMSOTf is undesirable, we continued the search of alternative promoter systems.





Entry	Conditions	Yield of 11
1	AgOTf (3.0 equiv), rt, 24 h	NR
2	AgBF ₄ (5.0 equiv), rt, 5 h	85%
3	Ag ₂ CO ₃ (1.0 equiv), TMSOTf (2.0 equiv), rt, 19 h	20%
4	Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), rt, 2 h	87%
5	NIS (2.0 equiv), TfOH (0.2 equiv), 0 °C-rt, 24 h	36%
6	NIS (4.0 equiv), TfOH (0.8 equiv), rt, 1 h	60%
7	NIS (4.0 equiv), TfOH (1.0 equiv), rt, 1 h	72%
8	NIS (2.0 equiv), TMSOTf (0.2 equiv), 0 °C-rt, 24 h	NR
9	NIS (4.0 equiv), TMSOTf (1.0 equiv), rt, 16 h	57%
10	NIS (4.5 equiv), TMSOTf (1.0 equiv), rt, 1.5 h	77%

Glycosidation of SIn donor **2** with acceptor **7** in presence of 2.0 equiv of NIS and 0.2 equiv of TfOH, a common promoter system used for the activation of alkyl/aryl thioglycosides,²⁴ in 1,2-dichloroethane (1,2-DCE) afforded disaccharide **11** only in a very modest yield of 36% (entry 5). Moreover, the reaction was very sluggish, appeared as something is hindering the activation of the SIn leaving group, and required 24 h to get to this stage. Increasing the amount of promoters, NIS to 4.0 equiv and TfOH to 0.8 equiv, again appealed as a possible solution. Under these reaction conditions, disaccharide **11** was obtained rather swiftly, in 1 h, in a significantly improved, albeit still unremarkable yield of 60% (entry 6). Further increase in the amount of TfOH to 1.0 equiv turned out to be the most advantageous for this promoter system. As shown in entry 7, disaccharide **11** was obtained in 72% yield. In a further search of the promoters, we replaced TfOH with TMSOTf. While somewhat similar, this modified promoter system allowed to achieve disaccharide **11** in 77% yield in 1.5 h. A gradual increase in the amounts of promoters (entries 8-10) showed that 4.5 equiv of NIS and 1.0 equiv of TMSOTf are required to achieve this result.

To expand the scope of this reaction, we extended our study to secondary glycosyl acceptors **8-10** (Figure 1). Glycosylation reaction of SIn glucosyl donor **2** with the secondary glycosyl acceptors **8-10** in presence of Ag_2CO_3 (1.0 equiv) and TMSOTf (4.0 equiv), conditions that worked best for the primary acceptor **7** (see Table 1) were also successful herein. As shown in Table 2, the corresponding disaccharides **12**,²⁰ **13**,¹⁹ and **14**²⁵ were obtained in commendable yields ranging between 69-79% (entries 1-3). Subsequently, we extended our study to glycosylation of per-benzylated donors **4** and **6** with primary and secondary acceptors **7-10**. This study included both silver-and iodonium-mediated pathways, and the reaction conditions were adjusted to account for differences in reactivity among the donor and acceptor combinations.

Surprisingly, only slightly reduced amounts of promoters were permitted for the activation of supposedly much more reactive (armed) per-benzylated glycosyl donors.²⁶ Selected key results of this study are summarized in Table 2.

Table 2. Expanding the scope of glycosylation with SIn donors: synthesis of disaccharides

	12-22	
Glycosy (Sc Glycos 7-10	I donors 2,4,6 theme 1) Activators MS 3Å, Solvent ROH yl acceptors (Figure 1)	$BxO \qquad OBx BxO \qquad BxO \qquad OBx Bx = Bn or Bz Disaccharides 12-22 (see Table)$
Entry	Donor + Acceptor, conditions	Product (yield, α/β ratio)
1	2 + 8 , Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), 0 °C-rt, 20 h, 1,2-DCE	$\frac{BzO}{OBz} \xrightarrow{OOBn} BnO_{OMe}$ 12 (69%, β only)
2	2 + 9 , Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), 0 °C-rt, 4 h, 1,2-DCE	$B_{ZO} \xrightarrow{OBz}_{BzO} \xrightarrow{OBn}_{BnO} \xrightarrow{OBn}_{BnO}$
3	2 + 10, Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), 0 °C-rt, 4 h, 1,2-DCE	$14 (79\%, \beta \text{ only})$
4	4 + 7, Ag ₂ CO ₃ (1.0 equiv), TMSOTf (3.0 equiv), 0 °C-rt, 2 h, DCM	Bno
5	4 + 7, NIS (4.0 equiv), TfOH (1.0 equiv), rt, 0.5 h, DCM	15 (76%, 1/1.2)
6	4 + 8 , Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), -70 °C-rt, 3 h, DCM	Bno Con Bno Bno Bno Bno Bno Bno Me 16 (68%, 1/1.1)
7	4 + 9 , Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), -70 °C-rt, 3 h, DCM	Bno Bno OBn 17 (70%, 1.4/1)

	8 4 + 10 8 -70 °C	0, Ag ₂ CO ₃ (1.0), TMSOTf (4.0 equiv), C-rt, 3 h, DCM	Bno Bno Bno OBn Bno OBn Bno OBn Bno OBn Bno OBn Bno OBn Bno Bno Bno Bno Bno Bno Bno Bno Bno B
9	6 + 7, Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), rt, 0.5 h, DCM	Bno OBn Bno Bno Bno Bno Bno Bno Bno Bno Bno Bno	
10	6 + 7, Ag ₂ CO ₃ (1.0 equiv), TMSOTf (3.0 equiv), 0 °C-rt, 3 h, DCM	19 (80%, 1/1.2)	
11	6 + 8, Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), -70 °C-rt, 2 h, DCM	$BnO_{BnO_{BnO}}^{OBn}$ BnO_{BnO_{BnO}}^{OBn} BnO_{BnO_{OMe}}^{OBn} 20 (54%, 6.0/1)	
12	6 + 9, Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), -70 °C-rt, 2 h, DCM	Bn0 Bn0 Bn0 Bn0 Bn0 Bn0 Bn0 Bn0 Bn0 Bn0	
13	6 + 10, Ag ₂ CO ₃ (1.0 equiv), TMSOTf (4.0 equiv), -70 °C-rt, 2 h, DCM	Bno Bno Bno Bno OBn 22 (75%, 2.0/1)	

 Being marginally more reactive than its per-benzoylated counterpart, benzylated donor **4** could be smoothly activated for the reaction with the primary acceptor **7** with Ag₂CO₃ (1.0 equiv) and the reduced amount of TMSOTf (3.0 equiv). As a result, disaccharide **15**²⁷ was obtained in 91% in 2 h ($\alpha/\beta = 1.1/1$, entry 4). This series of experiments was performed in dichloromethane as the reaction solvent that would allow to start reactions at a low temperature (*vide infra*). Benzylated donor **4** could also be activated with NIS (4.0 equiv) and TfOH (1.0 equiv), essentially the same conditions used for the activation of the per-benzoylated SIn donor. As a result, disaccharide **15** was obtained in 76% yield in 30 min ($\alpha/\beta = 1/1.2$, entry 5). We then investigated glycosidation of donor **4** with secondary glycosyl acceptors **8-10** in the presence of Ag₂CO₃ and TMSOTf. These

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reactions were slower, and to achieve faster reactions, we increased the amount of TMSOTf back to 4.0 equiv. To achieve higher yields, these reactions were started at -70 °C, and then allowed to slowly warm to rt. This series of experiments produced the corresponding disaccharides 16^{28} 17^{29} and 18^{30} in good yields of 68-81% albeit unremarkable stereoselectivity (α/β from 1.4/1 to 1/1.1, entries 6-8).

After that, we investigated glycosylations with SIn galactosyl donor **6** with the same series of glycosyl acceptors **7-10**. Glycosylation reaction of donor **6** with primary acceptor **7** in the presence of Ag₂CO₃ (1.0 equiv) and TMSOTf (4.0 equiv) afforded disaccharide **19**³¹ in 70% yield in 30 min ($\alpha/\beta = 1/1.3$, entry 9). Decreasing the amount of TMSOTf to 3.0 equiv afforded disaccharide **19** in an increased yield of 80% was observed with practically no change in stereoselectivity (entry 10). This reaction, however, required 3 h to complete, and to achieve practical rates with the secondary acceptors we increased the amount to TMSOTf to 4.0 equiv. Like in case of glucosyl donor **4**, glycosylations of galactosyl donor **6** with the secondary glycosyl acceptors **8-10** were started at -70 °C, and then allowed to slowly warm to rt. This series of experiments produced the respective disaccharides **20**,³² **21**,³³ and **22**³⁴ in yields ranging between 54-75% with preferential α -stereoselectivity ($\alpha/\beta = 1.7-6/1$, entries 11-13).

After completing these series of experiments, we were still puzzled by the fairly low reactivity of SIn glycosides that required greater excess reagents than even stable alkyl/aryl thioglycosides. The requirement for using excess reagent resulted in unusually prominent side reactions that accompanied many glycosylations. Side products observed included silylated acceptors, hemiacetals, $1 \rightarrow 1$ -linked disaccharides, and 1,6-anhydro sugars. To gain a better understanding of this glycosylation reaction and uncover its mechanism we turned our attention to performing a set of experiments monitored by NMR. First, we investigated the activation with NIS. For this

purpose, SIn donor **2** was dissolved in CDCl₃, the solution was transferred into a standard 5 mm NMR tube, and ¹H NMR spectrum was recorded (Scheme 2A). NIS (1.0 equiv) was added and ¹H NMR spectrum was recorded in 15 min showing the formation of **23** as the only product (Scheme 2B).

Scheme 2. NMR experiments with SIn donor 2 in the presence of NIS (1-4 equiv) to



observe the formation of 23 and 24

While somewhat unanticipated, the formation of such intermediate is not surprising since the 3position of the indole ring system is strongly nucleophilic and known to react easily with electrophiles of different kinds.^{35,36} Compound **23** was sufficiently stable to be isolated through column chromatography and fully characterized (see the experimental section for details). The NH signal in **23** was noted to shift downfield, and the identity of this proton was confirmed by a separate deuterium exchange experiment that indicated the remanence of an exchangeable hydrogen on the N atom of **23** (see the SI for further details). Upon addition of the second equiv

of NIS, ¹H NMR spectrum was recorded in 25 min showing the formation of a mixture of compounds (Scheme 2C). As suggested by the ¹H NMR spectrum, a partial conversion of compound **23** to a new compound, presumably **24**, took place. Only when a total 4.0 equiv of NIS was added to the NMR tube, ¹H NMR spectrum recorded after 1 h showed the complete formation of intermediate **24** with no traces of **23** remaining (Scheme 2D). This explains the need for multiple equivalents of NIS to activate the SIn leaving group. The formation of the activated sulfonium intermediate **24** is supported by a $\delta\Delta$ 1.4 ppm downfield chemical shift of the H-1 signal, as indicated in Scheme 2C.

Based on the extended NMR monitoring our current understanding of the NIS-promoted reaction mechanism is as follows. Upon addition of 4.0 equiv of NIS and TfOH to the reaction mixture containing SIn donor **2** in 1,2-DCE the first equivalent of NIS gets consumed by the electrophilic addition of the iodonium ion at the remote C-3 position of the SIn aglycone to afford a stable intermediate **23** (Scheme 3). The presence of TfOH (or TMSOTf) facilitates the formation of the iodonium ion from NIS. The additional NIS is needed to convert **23** into the activated species **24** that results in the leaving group departure followed by glycosylation. While glycosidation of benzoylated SIn donor **2** proceeds via the intermediacy of the acyloxonium intermediate leading to complete stereoselectivity, glycosidations of benzylated SIn donors **4** and **6** proceed via oxacarbenium ion intermediate. The formation of the latter intermediate explains poor stereoselectivity of many uncontrolled glycosylations taking place without the assistance of the neighboring group at C-2.³⁷

Scheme 3. Plausible mechanism of the NIS/TfOH-promoted reaction



To uncover the mechanism of glycosylation reactions proceeding under the cooperative silver salt-Lewis acid catalysis, we set up a series of experiments to monitor the interaction of SIn donor **2** with the promoter system by NMR. For this purpose, donor **2** was dissolved in CDCl₃, the solution was transferred into a standard 5 mm NMR tube, and ¹H NMR spectrum was recorded (Scheme 4A). TMSOTf (1.0 equiv) was added and ¹H NMR spectrum was recorded in 10 min showing the formation of thioimidate **25** (Scheme 4B). Formation of such a tautomer was somewhat unexpected. The same product was formed with other amounts of TMSOTf (up to 4.0 equiv). Thioimidate **25** was found to be stable in solution for at least one hour, it survives conventional aqueous work-up and evaporation. However, compound **25** tautomerizes back into SIn glycoside **2** during column chromatography on silica gel.

Scheme 4. NMR experiments with SIn donor 2 in the presence of TMSOTf and Ag₂CO₃ to

study the mechanism



When Ag_2CO_3 (1.0 equiv) was added to the NMR tube containing **25** produced from **2** with 1 equiv of TMSOTf, compound **25** quickly tautomerizes back to compound **2**. Shown in Scheme 4C is a silver complex of **2** wherein the complexation has presumably occurred via the N-atom of indole. This mode of complexation is supported by a $\delta \Delta 0.7$ ppm downfield chemical shift of the NH signal with practically no other changes observed in comparison to the uncomplexed **2** (Scheme 4A). The analogy is found in the mode of complexation taking place with other thioimidates. Thus, it was previously found that non-aromatic thioimidates, such as *S*-thiazolinyl (STaz),¹⁰ complex silver and other metals via the nitrogen atom.³⁸ This mode of complexation is known to result in the remote activation with silver^{39,40} or temporary deactivation with platinum or palladium salts.⁴¹ Conversely, aromatic thioimidates such as *S*-benzoxazolyl (SBox)⁹ and *S*-benzimidazolyl (SBiz)¹¹ complex silver strictly via the anomeric sulfur.⁴² This differential activation, remote versus direct, has allowed us to devise a thioimidate-only orthogonal strategy for oligosaccharide synthesis.⁴³

When Ag₂CO₃ (1.0 equiv) was added to the NMR tube containing **25** produced from **2** with 2.0 or 4.0 equiv of TMSOTf, imidate **25** remained intact. ¹H NMR spectrum recorded in 10 min showed the presence of compound **25** only, presumably as a complex with silver due to minor changes in chemical shifts observed (Scheme 2D). Since no glycosylation takes place until multiple equiv of TMSOTf are added, we believe that tautomerization of **2** to **25** needs to have occurred prior to glycosylation under these reaction conditions.

Based on extended NMR monitoring our current understanding of the reaction mechanism of glycosidation of 2 in the presence of TMSOTf and Ag_2CO_3 is as follows. In presence of excess of TMSOTf, glycosyl donor 2 is first tautomerized into its thioimidate counterpart 25. We believe that the occurrence of this intermediate is the key for the successful activation to take place under these reaction conditions. While the formation of **2-Ag** complex is possible, there is no feasible pathway for the SIn leaving group activation, neither remotely nor directly (Scheme 5). Silver carbonate then complexes with thioimidate 25 to produces complex 25-Ag that is not yet sufficiently ionized to cause the leaving group departure. As proposed in our previous study of the cooperative silver/acid catalysis with glycosyl halides, after the initial interaction of the donor with the silver salt, a strongly ionized species A is produced due to the interaction with an acid. This intermediate will then cause the remote SIn leaving group departure. Depending on the protecting group at C-2, the subsequent glycosylation proceeds via an acyloxonium (SIn donor 2) or oxacarbenium (SIn donors 4 and 6) ion. Differently from our previous studies with glycosyl halides, wherein the glycosylations were driven by a strong affinity of silver to halogens and the irreversible formation of the Ag-X bond, the activation of the SIn donors proceeding via the interaction of silver with the N-atom is significantly slower. It is also possible that silver

carbonate will react with excess TMSOTf first to generate a loosely bound silver cation species, which are then attacked by the *N*-atom of thioimidate **25** to produce the ionized intermediate.

Scheme 5. Plausible mechanism of the Ag₂CO₃/TMSOTf-promoted reaction



Given the specific set of reaction conditions needed for the activation of this new leaving group, the orthogonality of SIn donors in respect to other popular leaving groups, thioglycoside **26**¹⁵ and thioimidate **27**,⁴² was then investigated. For this purpose, we set up a series of comparative competition experiments wherein 1.0 equiv of SIn donor **4** was set to compete with 1.0 equiv other glycosyl donors for 2.0 equiv of acceptor **7** (Scheme 6). All reactions were stopped after 30 min, and all reaction components were isolated and characterized. First, we set up a comparative competition experiment wherein SIn donor **4** and ethylthio glycoside **26** were set to compete for acceptor **7** in the presence of NIS (1.2 equiv) and TfOH (0.2 equiv). These are typical reaction conditions for the activation of thioglycosides. Indeed, SEt donor **26** reacted entirely, whereas SIn donor **4** was recovered in the form of iodine and SEt adducts **28** and **29** that were isolated in the combined yield of 90% (Scheme 6A). This experiment ultimately confirmed slow and incomplete activation of the SIn glycosides under the reaction conditions common for the

activation of alkyl/aryl thioglycosides. Adduct **28** can be readily activated for subsequent glycosylation because it is an intermediate formed as the first step of the interaction of the SIn leaving group with the iodonium promoter. In the competition experiment, it acts as a trap for excess I⁺ remaining after the activation of the SEt leaving group. Upon this, adduct **29** was formed as a result of trapping the SEt group, and this compound can also be glycosidated under typical conditions for the SIn leaving group activation.

We then set up a comparative competition experiment wherein SIn donor 4 and ethylthio glycoside 26 were set to compete for acceptor 7 in the presence of Ag_2CO_3 and TMSOTf, newly developed reaction conditions for the activation of SIn glycosides. As a result, SIn donor 4 reacted completely, whereas SEt donor 26 was recovered nearly quantitatively (97% yield, Scheme 6B). This experiment ultimately confirmed that common thioglycosides cannot be activated under the reaction conditions that have been devised for the activation of SIn glycosides.

Scheme 6. Competition experiments of SIn glycoside 4 vs SEt and SBox donors 26 and 27



Finally, we set up a comparative competition experiment wherein SIn donor **4** and SBox imidate **27**⁴² were set to compete for acceptor **7** in the presence of 2 equiv of AgOTf. These are common reaction conditions of the SBox leaving group activation⁹ that were found practically ineffective with SIn glycosides, as determined over the course of the preliminary screening (*vide supra*, Table 1). As a result of this competition experiment, SBox donor **27** reacted completely, whereas

SIn donor **4** was recovered in 90% yield (Scheme 6B). This series of experiments demonstrated that SIn glycosides possess different glycosyl donor properties than both thioglycosides and thioimidates to which they are structurally related to.

In summary, we developed a new class of glycosyl donors, indolylthio glycosides. This new glycosyl donor can be activated using a range of activators. Although the activation of the SIn leaving group requires excess reagents, their reactivity profile is interesting. The activation process was studied by NMR and the increased understanding of the mechanism led to a discovery of orthogonality of the SIn leaving group versus thioglycosides and thioimidates. Further investigation of this leaving group in oligosaccharide synthesis, as well as structural and mechanistic studies are currently underway in our laboratory.

Experimental

General. The reactions were performed using commercial reagents and the ACS grade solvents used for reactions were purified and dried in accordance with standard procedures. AgOTf was co-evaporated at least twice with dry toluene, dried in *vacuo* and stored under dark for better yield of glycosylated product. Column chromatography was performed on silica gel 60 (70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 5% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH₂Cl₂ and ClCH₂CH₂Cl (1,2-DCE) were distilled from CaH₂ directly prior to application. Molecular sieves (3 Å), used for reactions, were crushed and activated in vacuo at 390 °C for 8 h in the first instance and then for 2-3 h at 390 °C directly prior to application. Optical rotations were measured at 'Jasco P-2000' polarimeter. ¹H NMR spectra were recorded in CDCl₃ at 300 MHz, ¹³C{¹H} NMR spectra were recorded at 75 MHz. The ¹H NMR chemical shifts are referenced to tetramethyl silane (TMS, $\delta_{H} = 0$ ppm) or CDCl₃

 $(\delta_{\rm H} = 7.26 \text{ ppm})$ for ¹H NMR spectra for solutions in CDCl₃. The ¹³C NMR chemical shifts are referenced to the central signal of CDCl₃ ($\delta_{\rm C} = 77.00 \text{ ppm}$) for solutions in CDCl₃. Anomeric purity or anomeric ratios were accessed or calculated by comparing of the integration intensities of the relevant signals in their ¹H NMR spectra. Accurate mass spectrometry determinations were performed using Agilent 6230 ESI TOF LCMS mass spectrometer.

1,3-Dihydro-2*H***-indole-2-thione (indoline-2-thione, HSIn)** was obtained from oxindole and P_2S_5 following the previously described protocol¹³ that was modified as follows. A mixture containing oxindole (500 mg, 3.76 mmol) and P_2S_5 (1.0 g, 4.6 mmol) in dry THF (25 mL) was stirred under argon for 10 min at rt. Sodium bicarbonate (631 mg, 7.5 mmol) was added portionwise, and the resulting mixture was stirred for 4 h at rt. After that, the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (~200 mL) and washed with water (4 x 50 mL). The organic phase was separated, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was dried in *vacuo* for 1 h then dissolved in hot methanol (ca 50 °C). The resulting solution was allowed to slowly cool to rt to afford the title compound as a yellow crystalline solid in 64% yield. Analytical data for HSIn were in accordance with that previously reported.¹³

H-Indol-2-yl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (2). HSIn (0.45 g, 3.34 mmol), anhydrous K₂CO₃ (0.46 g, 3.33 mmol) and 18-crown-6 (0.16 g, 0.61 mmol) were added to a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide¹⁴ (1, 2.0 g, 3.03 mmol) in dry acetone (50 mL), and the resulting mixture was stirred under argon at 50 °C for 3 h. After that, the solids were filtered off through a pad of Celite, rinsed successively with CH₂Cl₂ and the combined filtrate was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (~150 mL), washed with 10% aq. NaHCO₃ (25 mL) and water (2 x 25 mL). The organic phase

 was separated, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (toluene - ethyl acetate 1% gradient elution) followed by crystallization from diethyl ether-hexanes to afford the title compound as colorless crystals in 63% yield (1.39 g, 1.904 mmol). Analytical data for **2**: R_f 0.60 (ethyl acetate/hexane, 3/7, v/v); m.p. 204-205 °C (diethyl ether-hexanes); $[\alpha]_D^{22}$ -81.8 (*c* = 1.0, CHCl₃); ¹H NMR (300 MHz): δ 4.12-4.18 (m, 1H, $J_{5,6a}$ = 4.8, $J_{5,6b}$ = 2.6 Hz, H-5), 4.52 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.74 (dd, 1H, H-6b), 4.85 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 5.45 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.54 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.91 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 6.76 (s, 1H, =CH), 7.10-8.08 (m, 24H, aromatic), 9.08 (s, 1H, NH) ppm; ¹³C{¹H} NMR (75 MHz): δ 62.3, 68.6, 70.6, 76.6, 76.9, 77.4, 84.1, 111.1, 112.3, 119.8, 120.6, 121.5, 123.0, 127.7, 128.2 (x2), 128.3 (x2), 128.4 (x2), 128.5 (x2), 128.6 (x2), 128.9, 129.3, 129.6 (x2), 129.7 (x2), 129.8 (x2), 129.9 (x2), 133.2, 133.3, 133.5, 137.9, 164.9, 165.2, 165.7, 166.6 ppm; ESI-TOF [M + Na]⁺: calcd for [C₄₂H₃₃NO₉SNa]⁺ 750.1774; found: 750.1763.

H-Indol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (4). A mixture containing ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (26,¹⁵ 5.0 g, 8.55 mmol) and freshly activated molecular sieves (3 Å, 1.0 g) in CH₂Cl₂ (50 mL) was stirred under argon for 1 h at rt. Bromine (0.53 mL, 10.26 mmol) was added and the resulting mixture was stirred for 20 min at rt. After that, the volatiles were removed under reduced pressure, the residue was co-evaporated with dry toluene (2 x 20 mL) and dried in *vacuo* for 2 h. The resulting residue containing crude 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide **3** was dissolved in CH₂Cl₂ (60 mL), HSIn (1.4 g, 9.41 mmol), anhydrous K₂CO₃ (1.30 g, 9.41 mmol), and 18-crown-6 (0.45 g, 1.75 mmol) were added, and the resulting mixture was stirred under argon for 16 h at rt. The solids were filtered off through a pad of Celite and rinsed successively with CH₂Cl₂. The combined filtrate (~200 mL) as washed with water (50 mL), 10% aq. NaHCO₃ (250 mL), and water (2 x 50 mL). The organic phase was separated, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane 5% gradient elution) followed by crystallization from diethyl ether -hexanes to afford the title compound as colorless crystals in 60% yield (3.44 g, 9.27 mmol). Analytical data for **4**: R_f 0.55 (ethyl acetate/hexane, 1/4, v/v); m.p. 116-117 °C (diethyl ether-hexanes); $[\alpha]_D^{22}$ +159.8 (*c* = 1.0, CHCl₃); ¹H NMR (300 MHz): δ 3.29 (dd, 1H, $J_{6a,6b}$ = 10.2 Hz, H-6a), 3.48 (dd, 1H, $J_{4,5}$ = 8.8 Hz, H-4), 3.76-3.90 (m, 3H, H-2, 3, 6b), 4.44 (d, 1H, ²*J* = 11.0 Hz, CHPh), 4.56-4.82 (m, 7H, H-5, 3 x CH₂Ph, $J_{5,6a}$ = 8.3 Hz), 4.92 (d, 1H, ²*J* = 10.8 Hz, CHPh), 5.47 (d, 1H, $J_{1,2}$ = 5.2 Hz, H-1), 6.47-7.45 (m, 24H, aromatic), 6.60 (dd, 1H, =CH), 9.39 (s, 1H, NH) ppm; ¹³C{¹H} NMR (75 MHz): δ 69.6, 70.7, 72.2, 73.6, 75.0, 75.8, 77.9, 79.2, 82.3, 86.9, 108.0, 110.6, 119.5, 119.7, 122.0, 126.4, 127.4, 127.6, 127.8, 127.9 (x5), 128.0 (x5), 128.3 (x2), 128.4 (x4), 128.6 (x2), 137.2, 137.3, 137.7, 137.8, 138.4 ppm; ESI-TOF [M + H]⁺: calcd for [C₄₂H₄₂NO₅S]⁺ 672.2784; found: 672.2792.

H-Indol-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-galactopyranoside (6). Ethyl 2,3,4,6-tetra-*O*benzyl-1-thio-β-D-galactopyranoside¹⁶ (5.0 g, 8.55 mmol) and freshly activated molecular sieves (3Å, 1.0 g) in CH₂Cl₂ (50 mL) were stirred under argon for 1 h at rt. Bromine (0.53 mL, 10.26 mmol) was added and the resulting mixture was stirred for 20 min at rt.⁴⁴ After that, the volatiles were removed under reduced pressure, the residue was co-evaporated with dry toluene (2 x 20 mL), and dried in *vacuo* for 2 h. The residue containing crude 2,3,4,6-tetra-*O*-benzyl-α-Dgalactopyranosyl bromide **5** was dissolved in dichloromethane (60 mL), HSIn (1.40 g, 9.41 mmol), anhydrous K₂CO₃ (1.30 g, 9.41 mmol), and 18-crown-6 (0.45 g, 1.75 mmol) were added, and the resulting mixture was stirred under argon for 10 h at rt. The solids were filtered off through a pad of Celite and rinsed successively with CH₂Cl₂. The combined filtrate (~200 mL) as washed with water (50 mL), 10% aq. NaHCO₃ (250 mL), and water (2 x 50 mL). The organic phase was separated, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane 5% gradient elution) followed by crystallization from diethyl ether -hexanes to afford the title compound as colorless crystals in 52% yield. Analytical data for **6**: R_f 0.40 (ethyl acetate/hexane, 1/4, v/v); m.p. 187-188 °C (diethyl ether-hexanes); $[\alpha]_D^{22}$ +108.3 (c = 1.0, CHCl₃); ¹H NMR (300 MHz): δ 3.24 (dd, 1H, $J_{6a,6b}$ = 10.0 Hz, H-6a), 3.80-3.90 (m, 3H, H-3, 4, 6b), 4.40 (dd, 1H, $J_{2,3}$ = 5.5 Hz, H-2), 4.32-4.96 (m, 9H, $J_{5,6a}$ = 2.3 Hz, H-5, 4 x CH₂Ph), 5.67 (d, 1H, $J_{1,2}$ = 5.5 Hz, H-1), 6.67-7.51 (m, 24H, aromatic), 6.67 (dd, 1H, =CH), 9.57 (s, 1H, NH) ppm; ¹³C {¹H} NMR (75 MHz): δ 70.7, 72.5, 73.6, 73.7, 74.4, 74.8, 76.1, 79.2, 87.6, 108.1, 110.6, 119.4, 119.7, 121.9, 126.7, 127.4, 127.6 (x2), 127.7, 127.8 (x2), 127.9 (x5), 128.0, 128.3 (x4), 128.4 (x4), 128.7 (x2), 137.1, 137.8, 137.9 (x2), 138.4 ppm; ESI-TOF [M + H]⁺: calcd for [C₄₂H₄₂NO₅S]⁺ 672.2784; found: 672.2797.

General glycosylation procedures

Method A: Glycosylation in the presence of Ag_2CO_3 and TMSOTf. A mixture of a glycosyl donor (0.041-0.044 mmol), a glycosyl acceptor (0.037-0.040 mmol), and molecular sieves (3 Å, 80 mg) in 1,2-DCE or DCM (1.0 mL) was stirred under argon for 1 h at rt. The mixture was then cooled to 0 or -70 °C (see Tables), Ag_2CO_3 (0.041-0.044 mmol) and TMSOTf (0.165-0.178 mmol) were added, and the resulting mixture was stirred under argon for 1 h. After that, the external cooling was removed, the reaction mixture was allowed to warm to rt, and stirring was continued for the time indicated in Tables. The solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~30 mL) was washed with

H₂O (2 x 10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution) to afford the corresponding disaccharide. If necessary, further purification was accomplished by size-exclusion column chromatography on Sephadex LH-20. Method B: Glycosylation in the presence of NIS and TfOH or TMSOTf. A mixture of a glycosyl donor (0.041-0.044 mmol), a glycosyl acceptor (0.037-0.040 mmol), and molecular sieves (3 Å, 80 mg) in 1.2-DCE or DCM (1.0 mL) was stirred under argon for 1 h at rt. After that, NIS (0.165-0.178 mmol) and TfOH (0.041-0.044mmol) or TMSOTf (0.041 mmol) were added, and the resulting mixture was stirred for the time and temperature indicated in Tables. The solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~30 mL) was washed with 10% ag. Na₂S₂O₃ (2 x 10 mL) and H₂O (2 x 10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced

pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane gradient elution). If necessary, further purification was accomplished by size-exclusion column chromatography on Sephadex LH-20.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-Dglucopyranoside (11). The title compound was obtained from donor 2 and acceptor 7^{19} by general glycosylation procedure in 87% yield as a white amorphous solid. Analytical data for 11 was in accordance with that previously reported.²⁰

Methyl4-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (12). The title compound was obtained from donor 2 and acceptor 8¹⁹ by the

general glycosylation procedure in 69% yield as a clear syrup. Analytical data for **12** was in accordance with that previously reported.²⁰

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-Dglucopyranoside (13). The title compound was obtained from donor 2 and acceptor 9^{19} by the general glycosylation procedure in 78% yield as a clear syrup. Analytical data for 13 was in accordance with that previously reported.¹⁹

Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-Dglucopyranoside (14). The title compound was obtained from donor 2 and acceptor 10^{19} by the general glycosylation procedure in 79% yield as a clear syrup. Analytical data for 14 was in accordance with that previously reported.²⁵

Methyl6-O-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (15). The title compound was obtained from donor 4 and acceptor 7 by thegeneral glycosylation procedures in 91% yield ($\alpha/\beta = 1.1/1$) as a colorless foam. Analytical datafor 15 was in accordance with that previously reported.²⁷

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (16). The title compound was obtained from donor 4 and acceptor 8 by the general glycosylation procedure in 68% yield of 16 ($\alpha/\beta = 1/1.1$) as a clear syrup. Analytical data for 16 was in accordance with that previously reported.²⁸

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl- α -D-glucopyranoside (17). The title compound was obtained from donor 4 and acceptor 9 by the general glycosylation procedure in 70% yield ($\alpha/\beta = 1.4/1$) as a clear syrup. Analytical data for 17 was in accordance with that previously reported.²⁹

Methyl2-O-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)-3,4,6-tri-O-benzyl- α -D-glucopyranoside (18). The title compound was obtained from donor 4 and acceptor 10 by thegeneral glycosylation procedure in 81% yield ($\alpha/\beta = 1.2/1$) as a colorless foam. Analytical datafor 18 was in accordance with that previously reported.³⁰

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside (19). The title compound was obtained from donor 6 and acceptor 7 by the general glycosylation procedure in 70% yield ($\alpha/\beta = 1/1.3$) as a clear syrup. Analytical data for 19 was in accordance with that previously reported.³¹

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (20). The title compound was obtained from donor 6 and acceptor 8 by the general glycosylation procedure in 54% yield ($\alpha/\beta = 6.0/1$) as a clear syrup. Analytical data for 20 was in accordance with that previously reported.³²

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl- α -D-glucopyranoside (21). The title compound was obtained from donor 6 and acceptor 9 by the general glycosylation procedure in 62% yield ($\alpha/\beta = 1.7/1$) as a clear syrup. Analytical data for 21 was in accordance with that previously reported.³³

Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-3,4,6-tri-*O*-benzyl- α -D-glucopyranoside (22). The title compound was obtained from donor 6 and acceptor 10 by the general glycosylation procedure in 75% yield ($\alpha/\beta = 2.0/1$) as a clear syrup. Analytical data for 22 was in accordance with that previously reported.³⁴

¹H NMR monitoring experiments

SIn glycoside 2 in the presence of NIS. A solution of donor 2 (0.04 mmol) and NIS (0.04-0.16 mmol) in CDCl₃ (1.0 mL) was stirred in a round bottom flask under argon for 5 min at rt. The

resulting solution was quickly transferred into a standard 5 mm NMR tube and ¹H NMR spectrum was recorded at 15, 25, and 60 min time points. The recorded spectra are presented in Scheme 2 and the SI.

SIn glycoside 2 in the presence of TMSOTf. A solution of donor 2 (0.0206 mmol) and TMSOTf (0.0206-0.0824 mmol) in CDCl₃ (1.0 mL) was stirred in a round bottom flask under argon for 5 min at rt. The resulting solution was quickly transferred into a standard 5 mm NMR tube and ¹H NMR spectrum was recorded at 15, 25, and 45 min time points. The recorded spectra are presented in Scheme 4 and the SI.

SIn glycoside 2 in the presence of TMSOTf and Ag_2CO_3 . A solution of donor 2 (0.0206 mmol) and TMSOTf (0.0206-0.0824 mmol) in CDCl₃ (1.0 mL) was stirred in a round bottom flask under argon for 5 min at rt. After that, Ag_2CO_3 (0.0206 mmol) was added and stirring was continued for 5 min at rt. The solid was filtered off, the filtrate was transferred into a standard 5 mm NMR tube, and ¹H NMR spectrum was recorded at 0.16, 0.25, 0.41, 0.75, and 1 h timepoints. The recorded spectra are presented in Scheme 4 and the SI.

Competition experiments

Experiment A. A mixture of ethylthio glucoside **26** (26.1 mg, 0.044 mmol), SIn glucoside **4** (30 mg, 0.044 mmol), acceptor **7** (41.5 mg, 0.089 mmol), and molecular sieves (3 Å, 80 mg) in 1,2-DCE (1.0 mL) was stirred under argon for 1 h at rt. Triflic acid (8.0 μ L, 0.00894 mmol) and NIS (12.1 mg, 0.0536 mmol) were added, and the resulting mixture was stirred under argon for 30 min at rt. The solid was then filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~30 mL) was washed with 10% aq. Na₂S₂O₃ (2 x 10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated

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under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to produce **15** in 98% yield. Also recovered were compounds **28** (HRMS $[M+Na]^+$: calcd for $[C_{42}H_{40}INO_5SNa]^+$ 820.1570, found: 820.1596) and **29** (HRMS $[M+Na]^+$: calcd for. $[C_{44}H_{45}NO_5S_2Na]^+$ 754.2637, found: 754.2645).

Experiment B. A mixture of ethylthio glucoside **26** (26.1 mg, 0.044 mmol), SIn glucoside **4** (30 mg, 0.044 mmol), glucosyl acceptor **7** (41.5 mg, 0.089 mmol), and molecular sieves (3 Å, 80 mg) in 1,2-DCE (1.0 mL) was stirred under argon for 1 h at room temperature. Ag₂CO₃ (12.3 mg, 0.044 mmol) was added and the resulting mixture was stirred for 5 min at rt. After that, TMSOTf (32.4 μ L, 0.178 mmol) was added, and the resulting mixture was stirred under argon for 30 min at rt. The reaction was then quenched with triethyl amine (one drop). The solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~ 30 mL) was washed with H₂O (2 x 10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to produce **15** in 96% yield. Also recovered was thioglycoside **26** in 97% yield.

Experiment C. A mixture of S-benzoxazolyl glucoside $27^{42,45}$ (30.1 mg, 0.045 mmol), SIn glucoside **4** (30 mg, 0.045 mmol) glucosyl acceptor **7** (41.5 mg, 0.089 mmol), and molecular sieves (3 Å, 80 mg) in 1,2-DCE (1.0 mL) was stirred under argon for 1 h at rt. After that, freshly activated AgOTf (10.7 mg, 0.089 mmol) was added, and the resulting mixture was stirred under argon for 20 min at rt. The solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~ 30 mL) was washed with H₂O (2 x 10 mL). The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/

hexane gradient elution). to produce **15** in 96% yield. Also recovered was SIn derivative **4** in 90% yield.

X-ray crystal structure determination for compounds 2 and 6

The obtained crystals were mounted on a MiTeGen cryoloop in random orientations. For compound **2**, preliminary examination and data collection were performed using a Bruker X8 Kappa Apex II Charge Coupled Device (CCD) Detector system single crystal X-Ray diffractometer equipped with an Oxford Cryostream LT device. All data were collected using graphite monochromated Mo K α radiation (λ = 0.71073 Å) from a fine focus sealed tube X-Ray source. Preliminary unit cell constants were determined with a set of 36 narrow frame scans. Typical data sets consist of combinations of ϖ and ϕ scan frames with typical scan width of 0.5° and counting time of 10 seconds/frame at a crystal to detector distance of 4.0 cm.

For compound **6**, preliminary examination and data collection were performed using a Bruker Venture Duo Photon-II single crystal X-Ray diffractometer equipped with an Oxford Cryostream LT device. Data sets were collected using an Incoatec I μ S micro-focus source (Cu) with multi-layer mirror optics. Preliminary unit cell constants were determined from a set of 180° fast phi scan frames (1 sec exposure, 1° scan). Typical data sets consist of combinations of ϖ and ϕ scan frames with typical scan width of 1.0° and counting time of 1 to 5 seconds/frame at a crystal to detector distance of 3.7 cm.

The collected frames were integrated using an orientation matrix determined from the narrow frame scans. Apex II and SAINT software packages⁴⁶ were used for data collection and data integration. Analysis of the integrated data did not show any decay. Final cell constants were determined by global refinement of reflections harvested from the complete data set. Collected

data were corrected for systematic errors using SADABS⁴⁶ based on the Laue symmetry using equivalent reflections. Structure solution and refinement were carried out using the SHELXTL- PLUS software package.⁴⁷ The structures were solved by direct methods and refined successfully in the monoclinic space group, P2₁. Full matrix least-squares refinements were carried out by minimizing Σw (Fo2-Fc2)2. The non-hydrogen atoms were refined anisotropically to convergence. All hydrogen atoms were treated using appropriate riding model (AFIX m3). Absolute structure determination resulted in Flack-x parameters of 0.02(4) and 0.011(11) for compounds **2** and **6**, respectively. Complete listings of positional and isotropic displacement coefficients for hydrogen atoms and anisotropic displacement coefficients for the non-hydrogen

atoms are listed in the SI.

ASSOCIATED CONTENT

Supporting Information

Additional experimental details, characterization data, NMR spectra for all new and selected known compounds, tables of calculated and observed X-ray structure factors. This material is available free of charge via the Internet at

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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