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An Improved Approach to the Direct Construction of 2-Deoxy-β-Linked Sugars: Applications to Oligosaccharide Synthesis

Dina Lloyd and **Prof. Clay S. Bennett**

Department Department of Chemistry, Tufts University 62 Talbot Ave., Medford, MA 02155 (USA)

Abstract

A next-generation reagent-controlled approach for the synthesis of 2,6-dideoxy and 2,3,6-trideoxy sugar donors in good yield and high β-selectivity is reported. The use of *p*-toluenesulfonyl chloride and potassium hexa-methyldisilazide (KHMDS) greatly simplifies deoxy-sugar glycoside construction, and can be used for gram-scale glycosylation reactions. The development of this approach and its application to the construction of β-linked deoxy-sugar oligosaccharides are described.

Keywords

carbohydrates; diastereoselectivity; glycosylation; oligosaccharides; synthetic methods

The field of glycoscience has received considerable attention over the past decade, due in large part to the recognition of the important roles carbohydrates play in biology and medicine. This has, in turn, led to calls for the development of new methods for the synthesis of oligosaccharides, with the intent to make the field more accessible to the boarder biomedical research community.[1] Among glycosidic linkages, the construction of β-linked 2-deoxy-sugars remains particularly challenging.[2] The development of diastereoselective synthetic approaches to these molecules is of interest owing to their prevalence in many bioactive natural products. Over 3400 bacterial natural products are glycosylated,[3] many of which possess oligosaccharides composed of β-linked 2,6-deoxy-hexopyranoses (Figure 1).[4] Furthermore, altering the composition of these oligosaccharides has been shown to dramatically affect the bio-activities of these natural products, including mitigating toxicity.[5] Thus, methods for the stereoselective construction of β-linked 2-deoxy-sugars have the potential to aid the development of next-generation therapeutics.[6]

The major challenge in the construction of β-linked 2,6-dideoxy sugars is the lack of functionality at the C-2 position, which precludes the use of neighboring group participation to control selectivity in glycosylation reactions.[7] Without such assistance, glycosylation reactions with deoxy-sugar donors frequently provide products as a mixture of α,β-anomers.

Correspondence to: Clay S. Bennett.

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Conflict of interest

The authors declare no conflict of interest.

[8] This lack of control has led many researchers to develop elegant approaches for the stereospecific installation of β-linked 2-deoxy glycosyl-linkages.[9] Indirect methods and de novo[10] approaches can provide excellent levels of selectivity, however, both approaches require post-glycosylation modification of the products to afford native structures. This drawback has led to renewed interest in developing methods for the direct synthesis of β-linked 2-deoxy-sugars where selectivity is independent of the nature of the coupling partners.[11] Despite these efforts, a universal selective glycosylation method that uses inexpensive and easy-to-handle reagents has yet to emerge.

As part of an ongoing program to develop a toolkit for selective reagent-controlled methods for 2-deoxy-sugar synthesis,[12] we have studied the utility of glycosyl sulfonates for the stereospecific construction of β-linkage targets.[13] Specifically, we have found that by matching the sulfonate leaving group ability with the 2-deoxy sugars reactivity, it is possible to generate species that react selectively through an S_N2-like manifold.[14] During our attempts to apply our chemistry to oligo-saccharide synthesis, we encountered several limitations in our previous approaches. Specifically, the instability of reagents such as sulfonic anhydrides[15] led to problems with reproducibility and scalability. To address this issue, we initiated efforts to establish a method for glycosyl sulfonate generation that is more robust and reliable. To that end, we saw potential in examining the use of the inexpensive and easy to handle *p*-toluenesulfonyl chloride (TsCl) as a promoter for large-scale β-selective glycosylation reactions with 2-deoxy-sugars. Herein, we describe the evolution of this third-generation promotor system for β-selective glycosylation reactions and report its application to oligosaccharide synthesis.

Initially, we were concerned that the chloride counterion generated during activation could react with the glycosyl tosylate intermediate, leading to the formation of an unreactive glycosyl chloride.[12a] To assess the utility of the reagent for glycoside construction, we carried out side-by-side glycosylations comparing *p*-toluenesulfonic anhydride (Ts_2O) and TsCl in the reaction between donor **1** and *p*-methoxyphenol. Pleasingly, both reagents provided the β-glycoside **2** as a single diastereomer in 54 % and 56 % yield, respectively (Table 1). Increasing the scale of the reaction led to an increase in yield. Furthermore, we also found that superior results are obtained if the TsCl is recrystallized prior to use (Table 1, entry 3 vs. 4). Further studies revealed that the reaction could be performed on gram scale in the presence of either 2,4,6-tri-*tert*-butylpyrimidine (TTBP) or β-pinene[16] (Table 1 entries 8–10).

Having established that we could generate aryl glycosides with the reaction, we turned our attention to disaccharide formation. To this end, we evaluated the reaction between olivosides **3** and **4** (Table 2). On small scale, both TsCl and Ts_2O (Table 2, entries 1 and 2) afforded products with excellent β-selectivity. Upon scale up, however, the yield dropped precipitously when Ts_2O was used as the promoter (see the Supporting Information, Table S2.2.1). Increasing the activation time to 1 h, when TsCl was used as the promoter, led to a modest improvement in yield (Table 2, entry 2 vs. 3). On the other hand, increasing the reaction concentration resulted in an improved yield of the product, albeit with slight diminished β-selectivity (Table 2, entry 4). We also considered alternative proton scavengers, 2,6-di-*tert*-butylpyridine (DTBP), and β-pinene. Both species increased the

reaction yield, but eroded the selectivity further (Table 2, entries 5–6). This screening also revealed that a proton scavenger was necessary, as there was a marked decrease in selectivity when the reaction was carried out in the absence of one (Table 2, entry 7). Pleasingly, we found that pre-forming the reaction on close to gram scale afforded **5** in good yield and selectivity, demonstrating the advantages of the current protocol over our previous generation-approach (Table 2, entry 8).

With optimized conditions in hand, we next evaluated the scope of the reaction with a variety of donors and acceptors (Figure 2). Glycosylation of **1** with **4** under optimal conditions afforded disaccharide **14** as a single isomer in 75 % yield (Table 3). Furthermore, by shortening the activation time to 15 min and increasing the donor to acceptor ratio from 1.5:1 to 2:1 we were able to obtain β-oleandrosides **16**, **17**, and **18** in moderate to good yields (Table 3, entries 3–5). Again, the reactions could be scaled up without any loss in selectivity (Table 3, entries 6–8) Finally, it is interesting to note that the acceptor can be treated with base after addition to the activated donor without appreciable loss of selectivity, further illustrating the user-friendly nature of the approach (Table 3, entry 9 and 10).

We next turned our attention to the more reactive 2,3,6-tri-deoxy donor, **8**. Under our optimized conditions, the reaction proceeded in high yield, but with attenuated β-selectivity. Interestingly, scaling the reaction up to 3 g scale proceeded in much better selectivity (16:1 β:α, Table 4, entries 1 and 2). Reasoning that a bulkier and less reactive sulfonate would improve selectivity through the generation of a more stable intermediate, we next examined triisopropylbenzenesulfonyl,[17] chloride (TrisylCl) as a promoter. However, this reagent afforded the product with diminished selectivity (Table 4, entry 3). We next examined donor **9** in the reaction to see if a less armed sugar would improve selectivity. Contrary to our expectations, the activation of disarmed donor **9** with TsCl resulted in a reversal of selectivity (1:2.2 β:α) (Table 4, entry 4). In an effort to improve α-selectivity, we next examined using TrisylCl to activate **9**, as this promoter decreased β-selectivity with **8**. Indeed, activation of **9** with TrisylCl led to the production of **20** as a single α-anomer in 84 % yield (Table 4, entry 5). These latter conditions could also be used to produce disaccharides in moderate yields (Table 4, entries 6 and 7).

We next turned to variable-temperature (VT) NMR to study the mechanism of the reaction. Activating **6** in [D_8]THF with TsCl at −78 °C, led to the formation of a species with an anomeric proton signal at 6.0 ppm indicative of an α-glycosyl sulfonate[12a,e,13a,18] (see Supporting Information, Section S5.1). The ^{1}H–^{13}C heteronuclear single-quantum correlation (HSQC) NMR spectrum correlates the ^{1}H NMR spectrum singlet at 6.0 ppm to a ^{13}C NMR signal at 101.5 ppm, which is again consistent with an anomeric sulfonate. The tosylate species was stable at temperature up to −50 °C, above which it readily decomposed to the glycal (see Supporting Information, Section S5.2). This supports a mechanism where the donor is converted into an α-glycosyl sulfonate intermediate, which reacts predominantly through an S_N2-like manifold.[12e]

Having established the utility of the reaction in disaccharide construction, we turned our attention to using the chemistry for production of larger targets. We first examined the synthesis of the trisaccharide of FD-594 (Figure 1). To this end, selective removal of the

naphthylmethyl ether on **14** afforded disaccharide **23** (Scheme 1). In the subsequent glycosylation, we found that we had to increase the reaction concentration to 0.07 °, (see Supporting Information) however, we were pleased to find that the reaction between **6** and **23**, afforded trisaccharide **24** as a single β-anomer in 75 %.

We next focused on the construction of the tetrasaccharide fragment of kigamicin E, since this molecule also contains a labile β-linked 2,3,6-trideoxy-sugar (Figure 1). Initially, we examined a convergent [2+2] assembly of kigamicin E. To this end, disaccharide **16** was cleanly converted to donor **25** by removing the anomeric PMP group with cerium ammonium nitrate (CAN).[19] Similarly, acceptor **26** was generated from **17** using a combination of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and β-pinene (Scheme 2). Much to our disappointment, convergent glycosylation of **25** with **26** afforded **27** as a mixture of anomeric products in 50 % yield.[20] Reasoning that the loss in selectivity may be due to the diminished reactivity of the larger donor, we next examined a linear approach to the target. This would involve first synthesizing the trisaccharide of kigamicin D. This latter species could then be elongated to afford the tetrasaccharide of kigamicin E (Scheme 3). In the synthetic direction, activating donor **6** with *p*-toluenesulfonyl chloride followed by treatment with acceptor **26** afforded **28** as a single β-anomer in 58 % yield (Scheme 3). Removal of the naphthylmethyl ether from **28** was uneventful, revealing **29** in good yield. Finally, activation of **6** with potassium hexamethyl-disilazide (KHMDS) and TsCl followed by treatment with the potassium salt of **29** afforded tetrasaccharide **27** as a single isomer in 50 % yield (Scheme 3).

In summary, we have developed an improved third-generation reagent-controlled approach for deoxy-sugar oligosaccharide synthesis. Using *p*-toluenesulfonyl chloride to activate di-deoxy-sugar donors results in the formation of a species that reacts with acceptors in excellent to near perfect β-selectivity. Furthermore, highly sensitive 2,3,6-trideoxy-sugar substrates are also viable coupling partners using this current protocol. These latter species can be activated to react in either a highly α- or β-selective fashion, depending on the protecting group at C-4 and promoter (TrisylCl vs. TsCl) used in the reaction. Importantly, the chemistry is also readily scalable, and can be carried out using multi-gram quantities of donor. VT NMR studies revealed that the reaction proceeds through the formation of an α-glycosyl tosylate, which presumably reacts through an S_N2-like manifold with nucleophiles to afford β-linked products. The utility and robustness of the protocol was demonstrated in the stereospecific construction of tri- and tetrasaccharides found in the bioactive natural products FD-594 and kigamicin D and E. The application of this chemistry to more complex systems is currently under investigation in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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20. Similar loss of selectivity was seen during a test glycosylation of 25 with acceptor 10 (see Supporting Information, Section S4).

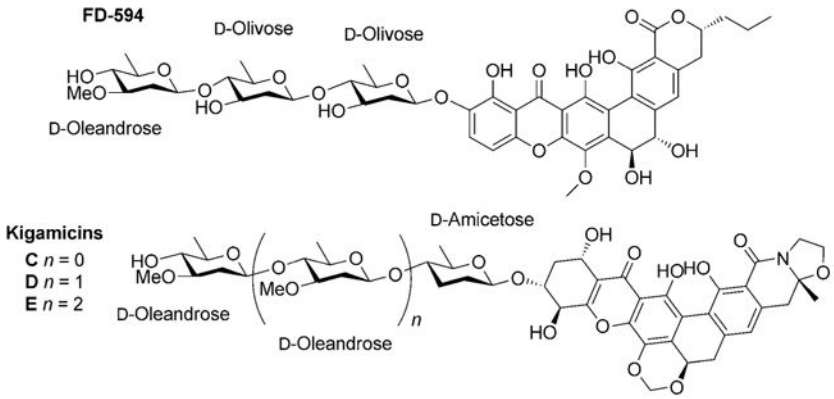


Figure 1.
Naturally occurring 2,6-deoxy and 2,3,6-deoxy sugars.

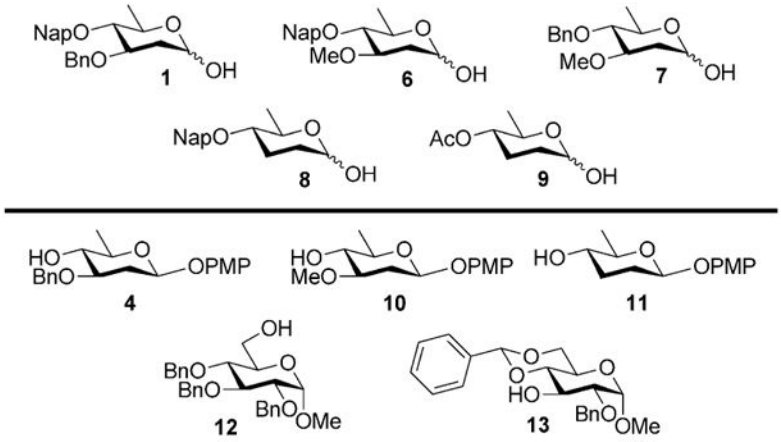
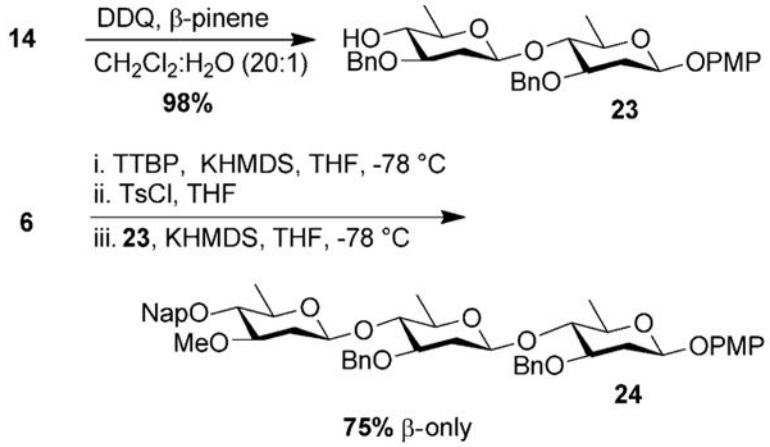
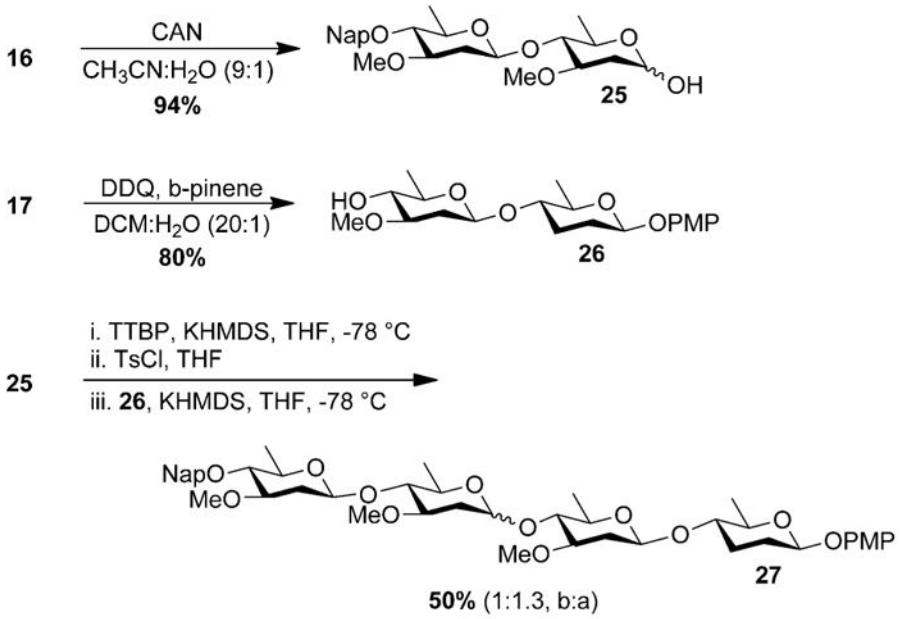


Figure 2.
Donors and acceptors used for substrate screening.

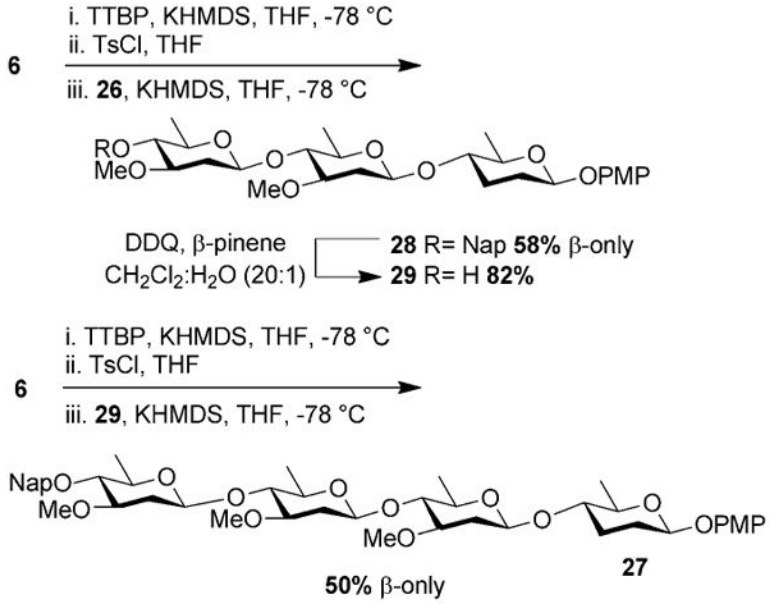


Scheme 1.
Synthesis of FD-594 trisaccharide **24**.



Scheme 2.

Convergent synthesis of kigamicin E tetrasaccharide **27**.

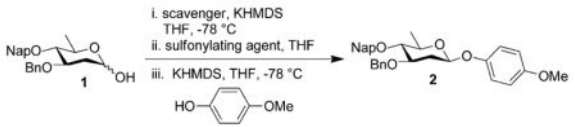


Scheme 3.

Linear synthesis of kigamicin D trisaccharide **28** and E tetraaccharide **27**.

Table 1

p -Toluenesulfonyl chloride screening with **1** and *p*-methoxyphenol.



Entry	Scavenger	Donor [g]	Acceptor [g]	Sulfonylating Agent	Yield [%][a]	β:α
1[b]	TTBP	0.14	0.03	Ts_2O	54	β-only
2[b]	TTBP	0.14	0.03	TsCl	56	β-only
3[b]	TTBP	0.42	0.09	TsCl	70	β-only
4	TTBP	0.42	0.09	TsCl	90	β-only
5	TTBP	1	0.22	TsCl	93	β-only
6	TTBP	2.3	0.5	TsCl	97	β-only
7	TTBP	4.5	1	TsCl	96	β-only
8	β-pinene	0.14	0.03	TsCl	99	β-only
9	β-pinene	2.3	0.5	TsCl	97	β-only
10	β-pinene	4.5	1	TsCl	96	β-only

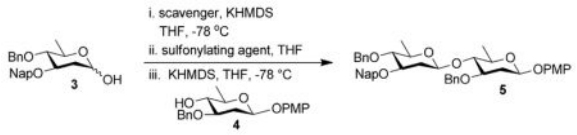
[a]Yield of isolated product.

[b]Sulfonylating agent used without recrystallization.

Nap = 2-naphthylmethyl; TTBP = 2,4,6-tri-*tert*-butylpyrimidine; Ts_2O = *p*-toluenesulfonic anhydride; TsCl = *p*-toluenesulfonyl chloride.

Table 2

Reaction optimization for disaccharide **5**.



	Scavenger	Sulfonylating Agent	Activation time [h]	[Activation] [°]	[Glycosylation] [°]	Yield [%][a]	β:α[b]
1	TTBP	Ts_2O	0.5	0.051	0.040	76	β-only
2	TTBP	TsCl	0.5	0.050	0.040	50	β-only
3	TTBP	TsCl	1	0.053	0.041	64	β-only
4	TTBP	TsCl	1	0.074	0.053	74	18:1
5	β-pinene	TsCl	1	0.074	0.053	78	15:1
6	DTBP	TsCl	1	0.074	0.053	71	16:1
7	—	TsCl	1	0.053	0.041	80	6.4:1
8[c]	TTBP	TsCl	1	0.075	0.054	60	β-only

[a]Yield of isolated product.

[b]The β:α ratio of the product after isolation.

[c]820 mg donor scale and 500 mg acceptor scale.

DTBP = 2,6-di-*tert*-butylpyridine; [Activation] = Donor concentration after addition of sulfonylating agent; [Glycosylation] = Donor concentration after addition of metalated acceptor.

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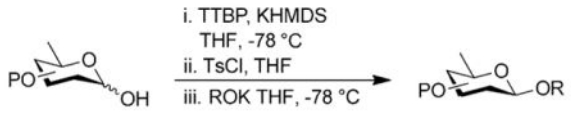
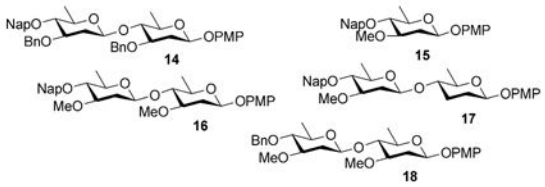
Table 3

Glycosylation reactions with various glycosyl donors and acceptors.



Entry	Donor	R′OK	Activation time [h]	Product	Yield [%][b]	β:α
1	**1**	**4**	1	**14**	75	β-only
2	**6**	PMP	0.5	**15**	87	β-only
3[c]	**6**	**10**	0.25	**16**	75	β-only
4[c]	**6**	**11**	0.25	**17**	55	β-only
5	**7**	**10**	1	**18**	70	β-only
6[c,d]	**1**	**4**	1	**14**	66	β-only
7[d]	**6**	**10**	0.25	**16**	62	β-only
8[d]	**6**	**11**	0.4	**17**	50	β-only
9[e]	**6**	**10**	0.25	**16**	66	β-only
10[f]	**6**	**10**	0.25	**16**	48	β-only



[a]Donor:acceptor ratio 2:1 unless otherwise noted.

[b]Yield of isolated product.

[c]Donor:acceptor ratio 1.5:1.

[d]500 mg acceptor scale.

[e]Added KHMDS immediately after addition of acceptor.

[f] Added KHMDS 3 h after addition of acceptor.

PMP = *p*-methoxyphenyl.

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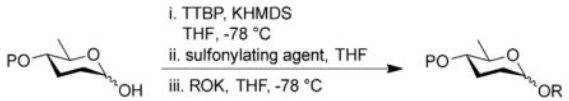
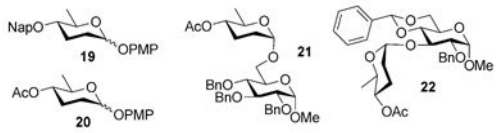
Table 4

Glycosylation of 2,3,6-trideoxy sugars **8** and **9** with various acceptors.



Entry	Donor	Acceptor	Sulfonylating Agent	Product	Yield [%][a]	β:α[b]
1	**8**	PMP	TsCl	**19**	80	8:1
2	**8**	PMP	TrisylCl	**19**	42	5:1
3	**9**	PMP	TsCl	**20**	60	1:2.2
4	**9**	PMP	TrisylCl	**20**	84	α-only
5	**9**	**12**	TrisylCl	**21**	27	α-only
6	**9**	**13**	TrisylCl	**22**	41	α-only



[a]Yield of isolated product.

[b]Selectivity determined by ^{1}H NMR spectroscopy.

[c]3 g donor scale and 930 mg acceptor scale.

TrisylCl = triiso-propylbenzenesulfonyl chloride.