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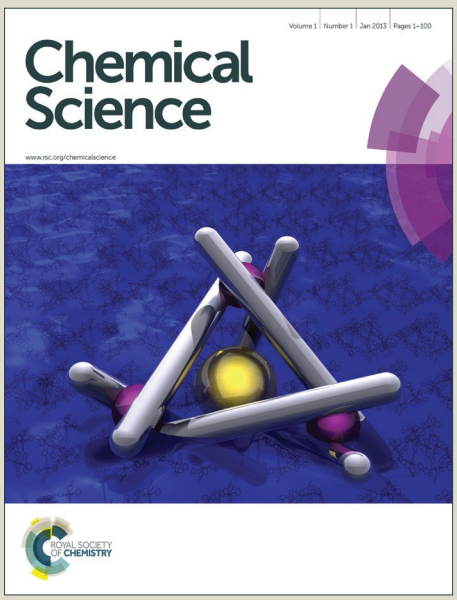

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ARTICLE

A Highly Diastereoselective "Super Silyl" Governed Aldol Reaction: Synthesis of α,β-Dioxyaldehydes and 1,2,3-Triols

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A highly diastereoselective approach for the synthesis of protected α,β-dioxyaldehydes derived from (*Z*)-tris(trimethylsilyl)silyl "super silyl" enol ethers is described. A general and highly *syn*-stereoselective aldol reaction directed by the "super silyl" group catalyzed by triflimide ($HNTf_2$) is developed providing α,β-dioxyaldehydes and 1,2,3-triol fragments which can be useful platform for the elaboration of natural and unnatural sugar derivatives.

Introduction

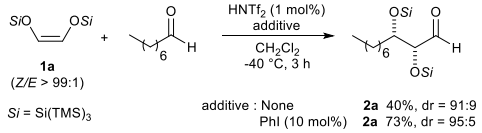
Polyols are among the most interesting motifs present in various natural and synthetic products. Over the past several decades organic synthesis have done great efforts to invent simpler and more efficient strategies to access stereodefined polyol motifs toward the synthesis of complex sugar frameworks. Because the majority of synthesis of molecules containing this motif require a multistep protocol for access, chemists have been attracted in creating multiple stereocenters in a one-pot procedure. Although there are numerous route to C-C bond forming, aldol reaction remains the most promising and straightforward method for creating two new adjacent stereogenic centers toward the construction of the required polyol subunits.[1,2]

Recently our group has actively investigated the Mukaiyama aldol reaction of tris(trimethylsilyl)silyl "super silyl" enol ethers for a highly diastereoselective synthesis of β-supersiloxyaldehydes and α-halo-β-supersiloxyaldehydes applying Lewis acid catalysis.[3] This efficient methodology allows for a rapid and stereoselective construction of mono-, bis- and trishydroxyaldehydes through mono, double and triple cross aldol processes respectively affording polyketide-like scaffolds which are particularly useful for an oriented construction of complex natural polyketides. In our continuous studies on Mukaiyama aldol reaction of super silyl enol ethers, we questioned whether a similar strategy might provide access to α,β-dioxygenated aldehydes which could be a useful building block for construction of complex sugar moiety.[4]

Results and discussion

Herein we describe the first highly diastereoselective aldol reaction with dioxy enol ethers to give protected α,β-dioxygenated aldehydes in moderate to good yields and with exclusively high *syn* selectivities.

Super silyl enol ether derived from silyloxy acetaldehyde [5] was prepared according to the general procedure recently developed in our laboratory.[2a] We began our studies by establishing optimal conditions for Mukaiyama aldol reaction of bissuper silyloxy enol ether **1a** with 1-octanal using 1 mol% of $HNTf_2$ as catalyst in dichloromethane at -40 °C (scheme 1).



Scheme 1. Influence of the additive on the aldol reaction. Yields of isolated aldehydes are shown. The dr ratios are determined from crude ^1H NMR.

We were pleased to find that the aldol adduct was obtained in high diastereoselectivity (dr = 91:9) but with moderate yield (40%). Thus, in an attempt to optimize the obtained results we performed the reaction in the presence of 10 mol% of iodobenzene which have previously been found very useful to increase the reactivity and the rate of aldol reaction.[3d] Gratifyingly, we found that the reaction works more efficiently and the adduct **2a** was obtained with much better yield (73%) and a slightly improved diastereoselectivity (dr = 95:5). Although we are not sure about the exact role of iodobenzene, we believe that it acts as a co-catalyst that stabilizes the silylenium cation formed *in situ*. Because the additive seemed to be playing a critical role in affecting the rate of the reaction, we conducted a ^{29}Si NMR study with the hypothesis that $[PhI\text{-}Si(TMS)_3]^+$ is the real active catalytic species. We first registered a reference ^{29}Si NMR spectra using a simple substrate test (allyltris(trimethylsilyl)silane) in presence of triflimide (Scheme 2, spectra (1)). We detected a first singlet corresponding to three trimethylsilyls that appears at -15.35 ppm and a second singlet corresponding to central silicon that appears at 4.61 ppm. Iodobenzene was then added to the NMR tube and a second ^{29}Si NMR spectra was registered after 45 min at room temperature.

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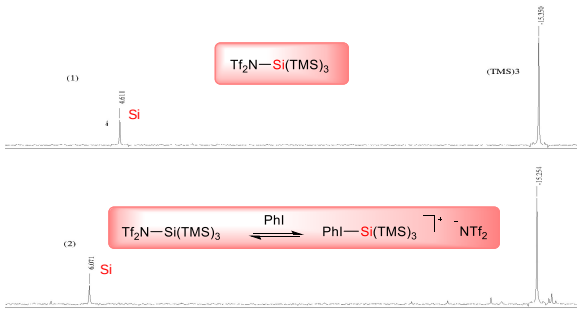
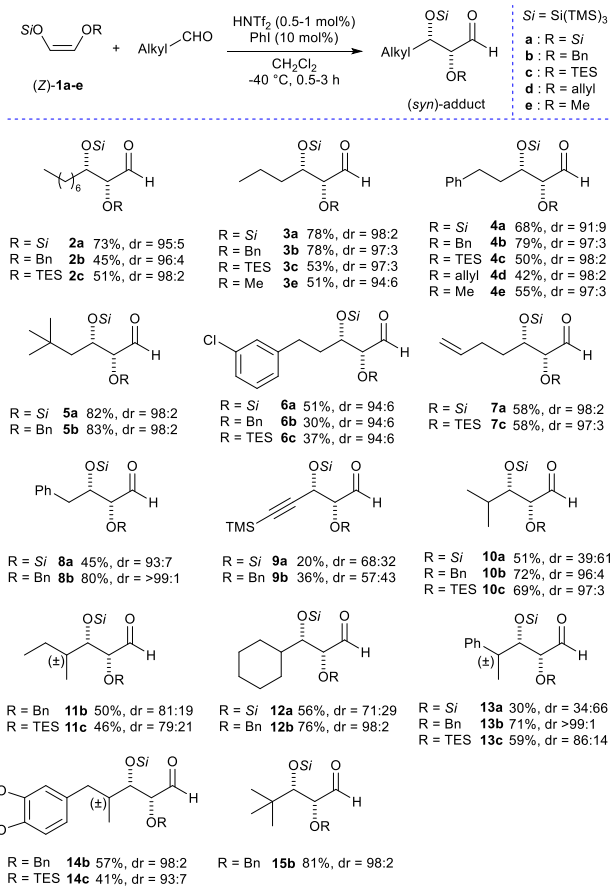
†Electronic Supplementary Information (ESI) available. CCDC 1409680 (**3a**) and 1409678 (**25**). For experimental procedures and full compound characterization, including NMR spectra and crystallographic data or other electronic formats see DOI: 10.1039/x0xx00000x



Scheme 2. ^{29}Si NMR Study on the Influence of iodobenzene on the aldol reaction. 1 equiv of iodobenzene was used. Experiments conducted in NMR tube in CD_2Cl_2 under nitrogen atmosphere and at room temperature.

Amazingly, we found that the second singlet was incredibly shifted up to 6.07 ppm (Scheme 2, spectra (2)). Surprised by the large effect that iodobenzene had on the outcome of the NMR experiment, we decided to perform other experiments with varying the stoichiometry and the reaction time. Interestingly, we found that the higher amount of iodobenzene is used the higher the silicon shift is obtained and the longer reaction time the more shifted singlet is detected (see Supporting Information). To the best of our knowledge, this is the first NMR proof of the role of organoiodide in Mukaiyama aldol reaction and the ^{29}Si NMR study was a proof of our principle considering $[PhI\text{-}Si(TMS)_3]^+$ as a more active catalytic species then $Tf_2N\text{-}Si(TMS)_3$.

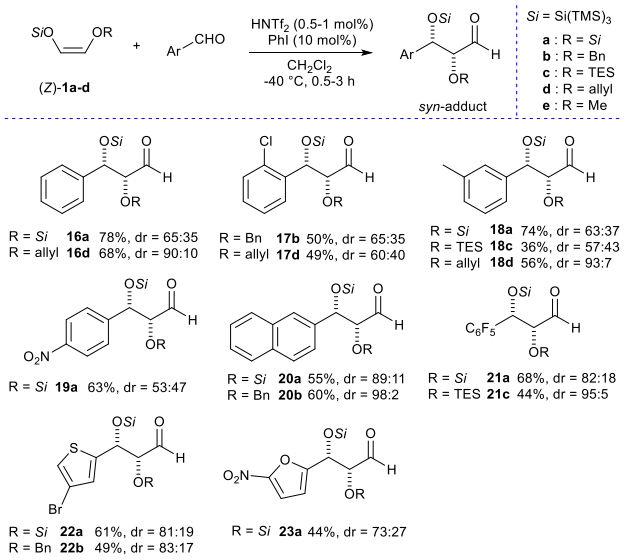
Satisfied with these results, we applied our general condition to the reaction of various supersilyl enol ethers with a broad array of aldehydes to afford protected α,β-dioxygenated aldehydes (Scheme 3). Most linear aliphatic aldehydes reacted very smoothly and selectively with super silyl enol ether **1a-e** providing the desired α,β-dioxyaldehydes (**2-8**) in moderate to high yields (up to 83% for compound **5b**) and with excellent and exclusive *syn*-selectivities (up to 98:2). Fortunately, the major diastereomer of compound **3a** was crystalline, and the *syn* stereochemistry was directly determined from X-ray analysis.[6] Aldehyde bearing an unsaturation (alkynyl group) in alpha of the carbonyl group was also tested and found to be rather sluggish with super silyl enol ethers **1a** and **1b** to afford the corresponding adducts **9a** and **9b** respectively with low yields and poor selectivity. We next investigated aliphatic aldehydes bearing an additional substitution in alpha of the carbonyl which were also tolerated but with moderate yields (up to 51%) and selectivities (up to 71:29 dr) (**10a, 12-13a**) due to the presence of the extraordinarly bulky silyloxy group. Nevertheless when we tested these branched aldehydes with a less bulky silyl enol ether by substitution of one of the super silyloxy groups with a benzyloxy (**1b**) or a triethylsilyloxy group (**1c**) we found that the previously obtained yields and diastereoselectivities were incredibly improved (**10a** *vs* **10b** and **10c**, **12a** *vs* **12b**, **13a** *vs* **13b** and **13c**). (*Z*)-1-Supersilyloxy-2-benzyloxy enol ether **1b** reacted as expected with remarkably high selectivities (up to >99:1) and better yields (up to 72%) obtained in almost all products (**2-15**). Notably, pivalaldehyde, which was unreactive with other super silyl enol ethers, was found to react smoothly with (*Z*)-1-supersilyloxy-2-benzyloxy enol ether **1b** to afford the corresponding aldol adduct **15b** with excellent yield and diastereoselectivity (81%, dr = 98:2). On the other hand, (*Z*)-1-supersilyloxy-2-triethylsilyloxy enol ether **1c** was found to proceed less effectively affording the corresponding aldol adducts with diminished yields, probably due to



Scheme 3. Synthesis of protected α,β-dioxyaldehydes: substrate scope of aliphatic aldehydes. Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale. Yields of isolated aldehydes are shown. The dr are based on the integration of the ^{1}H NMR signals of crude material. The attribution of *syn* and *anti*-ratio was based on the coupling constant of characteristic protons.

the competitive reaction of the triethylsilyloxy group with our catalyst although we did not observe the formation of the corresponding regioisomer, and with no remarkable changes on diastereoselectivity ratios obtained with **1a** or **1b**. Subsequently, additional supersilyl enol ethers bearing allyloxy (**1d)** or methoxy (**1e)** groups were also briefly investigated. We subjected (*Z*)-1-allyloxy-2-supersilyloxy enol ether **1d** and (*Z*)-1-methoxy-2-supersilyloxy enol ether **1e** to our optimized reaction conditions, affording the corresponding desired aldol adducts with comparable yields and diastereoslectivities.

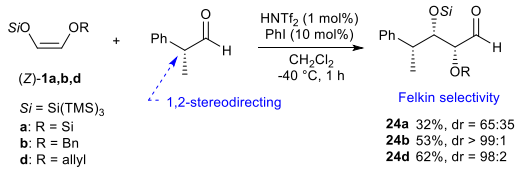
After the exploration of the scope of aliphatic aldehydes, we next turned our attention to the scope of aromatic aldehydes which were found to be more challenging. When we first investigated the reactivity of benzaldehyde with **1a** using 1 mol% of triflimide catalyst without any additive, we found that the reaction did not proceed and only trace amount (<5%) of the desired adduct was detected. However, when the reaction was performed with 10 mol% of iodobenzene, the results were amazingly improved and the reaction provided the desired aldol adduct **16a** in high yield (78%) but with moderate diastereoselectivity (Scheme 4). Despite the encouraging results regarding the increased yield using iodobenzene, all other attempts to improve the diastereoselectivity ratio for aromatic



Scheme 4. Synthesis of protected α,β-dioxyaldehydes: substrate scope of aromatic aldehydes. Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale. Yields of isolated aldehydes are shown. The *dr* are based on the integration of the ^{1}H NMR signals of crude material. The attribution of *syn* and *anti*-ratio was based on the coupling constant of characteristic proton.

aldehydes failed probably due to the presence of the two very bulky super silyl groups nearby. Even so, we were interested in examining the scope of aromatic substrates with our super silyl enol ethers. The reaction with **1a** was found to have poor selectivity (**16a**, **18-23a**) due to steric hindrance with the two silyloxy groups. Nevertheless, we were delighted to find that diastereoslectivity could be improved up to 98% (for compound **20b**) starting from **1b** and up to 93% (for compound **18d**) starting from **1d**. Then we considered the use of heteroaromatic aldehydes and experiments have shown that an electron-withdrawing group on the heteroaromatic ring is necessary for the reaction to proceed. Our scope was then extended and compounds **22a-b** and **23a** were obtained in acceptable yields and diastereoselectivities. Worthy to note that all the protected *syn*-α,β-dioxyaldehydes obtained are stable in almost all cases and can be kept for weeks in the freezer since these compounds are known to be rather sensitive to both elimination and epimerisation.

The scope of the reaction was further examined by reacting optically pure aldehyde with different super silyl enol ethers. In this case, it is known that the stereochemical outcome of the reaction can be controlled by the chirality of the substrate (1,2-asymmetric induction).[7,8]

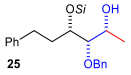
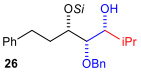
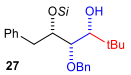
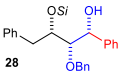
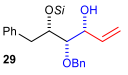
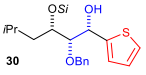
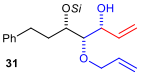
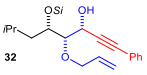
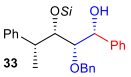
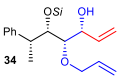
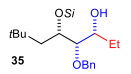
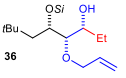


Scheme 5. 1,2-Stereodirected aldol reaction. Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale. Yields of isolated aldehydes are shown. The *dr* are based on the integration of the ^{1}H NMR signals of crude material. The attribution of *syn* and *anti*-ratio was based on the coupling constant of characteristic protons.

Indeed, the use of (*R*)-2-phenylpropanal exhibited as expected a high Felkin control in conjunction with *syn* selectivity to afford **24a,b,d** with three adjacent stereocenters in excellent diastereoselectivity ratios (up to >99:1 *syn-syn* for compound **24b**) (Scheme 5).[9]

Next, we investigated the possibility of subsequent one-pot sequential transformation of the obtained protected α,β-dioxygenated aldehydes (Table 1). The addition of alkyl, vinyl, alkynyl, thiophen-2-yl or aryl Grignard reagents to the crude material proceeded smoothly to afford trishydroxy products **25-34** with good to excellent yields (50-84%) and exceptionally high *syn-syn* diastereoselectivities (>99:1:0) which was confirmed by single crystal X-ray analysis of triol **27**.[10] In a same fashion as in scheme 5, we considered the use of aldehyde with a defined α-stereocenter for a 1,2-asymmetric induction investigation. After reaction of (*R*)-2-phenylpropanal with super silyl enol ether **1b** and addition of the phenylmagnesium chloride we obtained the desired triol **33** in moderate yield (50%) and diastereoselectivity (dr = 83:17:0).

Table 1. Diastereoselective one-pot sequential reactions.[a]

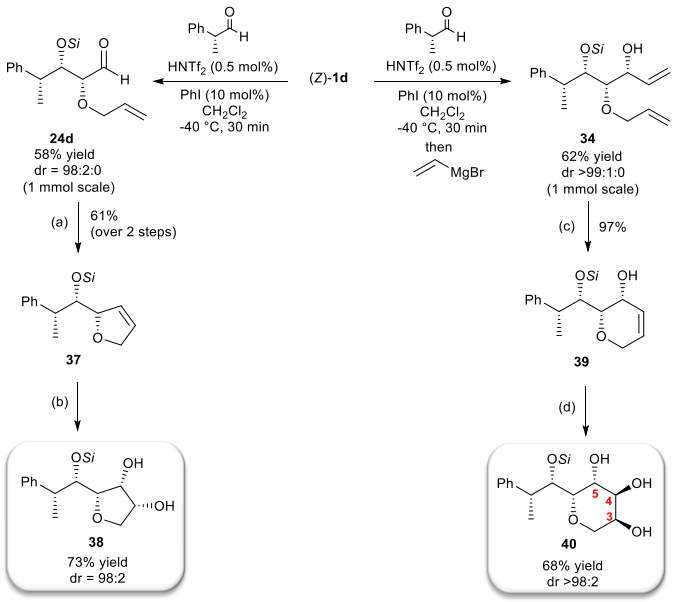
entry	R	R'	nucleophile[b]	major product	%yield[c] (dr)[d]
1	Bn	CH_2CH_2Ph	MeMgBr	 **25**	84% (dr >99:1:0)
2	Bn	CH_2CH_2Ph	*i*PrMgBr	 **26**	81% (dr >99:1:0)
3	Bn	CH_2Ph	*t*BuMgBr	 **27**	78% (dr >99:1:0)
4	Bn	CH_2Ph	PhMgCl	 **28**	59% (dr >99:1:0)
5	Bn	CH_2Ph		 **29**	68% (dr >99:1:0)
6	Bn	$CH_2CH(CH_3)_2$		 **30**	75% (dr >99:1:0)
7	Allyl	CH_2CH_2Ph		 **31**	82% (dr >99:1:0)
8	Allyl	$CH_2CH(CH_3)_2$		 **32**	52% (dr = 88:12:0)
9	Bn		PhMgCl	 **33**	50% (dr = 83:17:0)
10	Allyl			 **34**	63% (dr >99:1:0)
11[e]	Bn	$CH_2(CH_3)_3$	EtLi	 **35**	33% (dr >99:1:0)
12[e]	Allyl	$CH_2(CH_3)_3$	EtLi	 **36**	36% (dr >99:1:0)

[a] Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale. [b] 1.5 equiv of nucleophile was used. [c] Yields of isolated products are shown. [d] The dr are based on the integration of the ^{1}H NMR signals of crude material. [e] The reaction was slowly warmed to -20 °C after addition of 2.0 equiv of nucleophile.

Then we decided to test the more reactive (Z)-supersilyloxy-2-allyloxy enol ether **1d** and introduce an additional vinyl group as it is a rather valuable handle for further transformations. By the addition of vinyl Grignard reagent we were delighted to easily isolate the synthetically useful vinylic triol **34** generating three new adjacent stereocenters in a one-pot sequential manner in 63% yield and excellent all-*syn* diastereoselectivity (>99:1:0). Moreover, the reaction was also successful using the lithiated nucleophile EtLi affording the desired alkyl triols **35** and **36** in high diastereoselectivity but with dramatically decreased yields (33% and 36% respectively).

Inspired by the important skeleton of the vinylic all-*syn* triol **34** and in an attempt to further probe the utility of our highly diastereoselective one-pot sequential aldol reaction, we targeted pentose and hexose-like scaffolds which are usually difficult to access without employing natural sugar as starting material.[11] We first applied our strategy to establish the desired α-allyloxy-β-supersilyloxyaldehyde **24d** which was obtained at a slightly dropped yield (58%) on 1 mmol scale but with no loss of selectivity (98:2 *syn*-*syn*). An olefination through Wittig reaction and ring closing metathesis using Grubbs second generation catalyst yielded the five member ring compound **37** in 61 % (over 2 steps). The last step of asymmetric dihydroxylation was performed by optimal conditions using catalytic AD-mix-β in biphasic solution at 0 °C for four days [12] which afforded a single diastereomer of **38** in 73% yield containing five adjacent stereocenters in excellent all-*syn* selectivity (scheme 6). The stereochemistry of compound **38** was determined based on ^{1}H, NOE and NOESY experiments (see the Supporting Information) in comparison with literature.

Finally, we considered the possibility of hexose-like scaffold construction, which can be a useful building block to access complex natural and unnatural sugar target. First we employed our highly diastereoselective Lewis acid catalyzed one-pot sequential aldol scaled-up reaction (1 mmol scale) starting from (*R*)-2-phenylpropanal and silyl enol ether **1d** followed by a nucleophilic addition of vinyl magnesium bromide to obtain the desired vinylic triol **34** with no loss of reactivity or diastereoselectivity (62%, 99% dr). Next, a very low loading of the Grubbs second generation catalyst (2 mol %) gave access to the six membered ring **39** in excellent yield (97%). A quick optimization of the asymmetric dihydroxylation step (see Supporting Information) showed that cis-osmilation using osmium tetroxide in presence of excess of N-methylmorpholine N-oxide provided the desired hexose-like structure.[13] Thus, compound **40**, containing six adjacent stereocenters, was obtained in 68% yield and with an exclusive 4,5-*anti* stereochemistry. The determination of the stereochemistry of the latter compound was based on the optimization reactions where we obtained the same single isomer using both chiral AD-mix-α or β with comparable selectivity but with a slower reaction rate (50 % conversion after 4 days) which can be explained by the preferred attack of osmium from opposite side of the free hydroxy group present in **39**. In addition, a very high coupling constant value ($J_{4\text{-}5}$ >10.6 Hz) was detected which emphasize an *anti*-like relationship between C4-H and C5-H.[14]



Scheme 6. Synthesis of pentose and hexose-like scaffolds. (a) (1) CH_3PPh_3, *n*-BuLi, THF (2) Grubbs 2nd generation (2 mol%), CH_2Cl_2, 40 °C, 2 h (b) (1) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0°C, 4 d (c). Grubbs 2nd generation (2 mol%), CH_2Cl_2, 40 °C, 2 h (d). OsO_4, NMO, *t*-BuOH, acetone/H_2O (1.7:1), r.t, 12 h.

Conclusions

In summary, a very useful strategy to generate synthetically important protected *syn*-α,β-dioxyaldehydes using Lewis acid catalyst has been described. To the best of our knowledge, this is the first synthesis of α-hydroxyaldehydes using Mukaiyama aldol reaction. Furthermore, ^{29}Si NMR study was performed providing the first proof of the role of iodobenzene as additive in increasing the reactivity of the active silylenium cation formed *in situ*. Since the ability of using different hydroxy protecting groups in the same molecule is an attractive tool to discriminate among chemically similar hydroxyl groups, silyloxy, benzyloxy, triethylsilyloxy, allyloxy and methoxy have been proved to be suitable for the construction of α,β-dioxyaldehydes and 1,2,3-triols. Various nucleophiles were found to react smoothly in a sequential manner allowing for a highly stereoselective construction of all-*syn* 1,2,3-triols. We have finally demonstrated the utility of our methodology being a key step for an elegant construction of pentose and hexose-like scaffolds. Further applications using super silyl governed aldol reactions targeting complex sugar construction are currently underway in our laboratory and will be reported in due course.

Acknowledgements

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Notes and references

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