Umpolung

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Direct Umpolung of Glycals and Related 2,3-Unsaturated *N*-Acetylneuraminic Acid Derivatives Using Samarium Diiodide**

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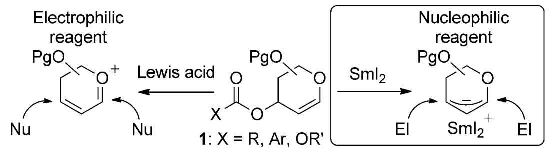
In memory of Robert (Robin) J. Ferrier and Jean-Louis Namy

Abstract: *The umpolung of glycals with samarium diiodide offers a simple route to novel carbohydrate-derived nucleophilic reagents in a single step using a readily available reductant. The corresponding allyl samarium reagent that arises from the hexose series reacts with ketones at the C3 position with high stereoselectivity; carbon–carbon bond formation takes place only anti to the substituent at the C4 position of the dihydropyran ring. For the sialic acid series, the completely regio- and stereoselective coupling process of the samarium reagent occurs at the anomeric carbon atom and provides a new approach to the α-C-glycosides of N-acetyl neuraminic acid.*



Scheme 1. Electrophilic or nucleophilic intermediates from glycals (1,5-anhydrohex-1-enitols) **1**. El = electrophile, Nu = nucleophile, Pg = protecting group.

Glycals (1,5-anhydrohex-1-enitols)[1] are carbohydrate derivatives that are extensively used for the preparation of important complex carbohydrates and glycoconjugates as well as non-carbohydrate natural products,[2] most notably through a Lewis acid induced allylic oxocarbenium ion that reacts with appropriate nucleophiles mainly at the anomeric center (known as the Ferrier I rearrangement; Scheme 1).[3] These useful substrates could also provide new types of nucleophilic carbohydrate-derived allylation reagents by polarity inversion (umpolung). However, such a reaction has not been reported to date. Using samarium diiodide as the reducing agent,[4–6] existing methods typically rely on the umpolung of preformed electrophilic palladium[7] (or iridium)[8] π-allyl complexes, as reported for simple allylic alcohol derivatives (esters, carbonates, phosphates).

Herein, we reveal that samarium diiodide alone can perform the direct and selective umpolung of glycals without the need for intermediary π-allyl transition-metal complexes.[9] This was demonstrated for the coupling reaction with appropriate carbonyl compounds under Barbier conditions. Furthermore, we show that the high regio- and stereoselectivity of this transformation can be fine-tuned by the structure of the substrates.

The direct reductive coupling of such substrates was initially studied with simple dihydropyranyl allylic esters. Therefore, treatment of acetate **3** or benzoate **4**[10] with SmI_2 alone at room temperature in the presence of a carbonyl compound provided only (entries 1–5 and 7, Table 1) or very predominantly (entries 6 and 8–10) the C4-coupling products **5a**–**f**. The highest yields were obtained with allylic benzoate **4** (entries 2, 3, 5, 7, and 9; 77–95% yield), suggesting that this group was first reduced to generate the initial allylic radical intermediate. The intracyclic oxygen atom of the dihydropyran ring is essential for the reaction to occur as allylic cyclohex-2-enyl acetate did not react under identical reaction conditions.[9b,11]

This procedure was then extended to more functionalized glycals. Surprisingly, commercial tri-*O*-acetyl-D-glucal did not react under the above conditions, which revealed that the reduction of the allylic acetate in this substrate was significantly more difficult than for dihydropyran substrates. However, orthogonally protected D-glucal derivatives **7b**–**e**, which are equipped with an allylic carbonate,[9a] all reacted with SmI_2 at room temperature under Barbier conditions, giving exclusively the C3-products **8a**–**g** (carbohydrate numbering) in 54–63% yield (entries 2–8, Table 2). Only di-*O*-benzyl substrate **7a** was very reactive (reaction at 0 °C for 2 h), but

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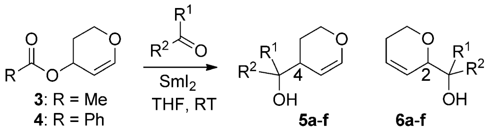
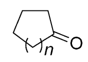
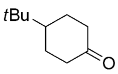
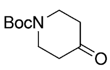
Table 1: SmI_2-induced umpolung of dihydropyranyl allylic esters **3** and **4**.[a]



Entry	Substrate	Ketone		C4-Adduct (yield)[b]	C2-Adduct (yield)[b]
1	**3**		$n=2$	**5a** (64%)	**6a** (<1%)
2	**4**		$n=2$	**5a** (77%)	**6a** (<1%)
3	**4**		$n=1$	**5b** (82%)	**6b** (nd)
4	**3**		$n=0$	**5c** (51%)	**6c** (<1%)
5	**4**		$n=0$	**5c** (87%)	**6c** (<1%)
6	**3**			**5d** (69%)[c]	**6d** (6%)
7	**4**			**5d** (95%)[c]	**6d** (nd)
8	**3**			**5e** (61%)	**6e** (6%)
9	**4**			**5e** (86%)	**6e** (10%)
10	**4**	pentan-3-one		**5f** (68%)	**6f** (10%)

[a] Conditions: SmI_2 (3 equiv), ketone (2 equiv), THF, 2 h, room temperature. [b] Yield after purification by column chromatography on silica gel. [c] Obtained as a 1:2.6 mixture of isomers. Boc = *tert*-butyloxycarbonyl, nd = not detected. Pyran numbering is used.

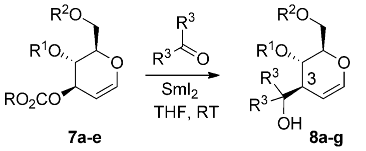
provided a low 33% yield of **8a** (entry 1) because of the competitive formation of unidentified side products.

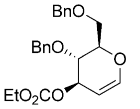
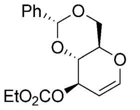
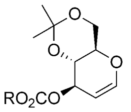
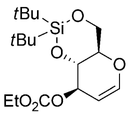
The reduction rate of **7b–e** was also much slower than above (1–2 days versus 2 h for the dihydropyrans; Table 1). Remarkably, all homoallylic alcohols **8a–g** were formed as single C3-regioisomers with the 3,4-*trans* configuration only, for example, with an overall retention of configuration at the C3 position. This *trans* relationship with an equatorial orientation of the newly formed C–C bond was determined by ^1H NMR analysis (strong nuclear Overhauser effect (nOe) between the H3 and H5 hydrogen atoms and large $J_{3,4}$ values of 8.6–9.4 Hz).

This study was also conducted with the D-galactal derivatives **9a** and **9b** to identify the structural features that control the stereochemical outcome of the reaction (Scheme 2). Again, the homoallylic alcohols **10a** and **10b** were formed as single C3-regioisomers from **9a** and **9b** with the 3,4-*trans* configuration only, for example, with an overall inversion of configuration at the C3 position. The reductive coupling of isopropylidene derivative **9b** was very slow (21% yield after 3 days with 44% of recovered starting material **9b**).[12]

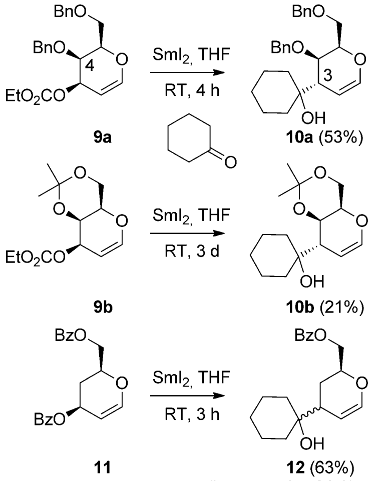
The chiral center at the C4 position strictly controls the stereochemical outcome of the coupling reaction as the trapping of the allylic samarium species occurred *anti* to the substituent at the C4 position. This was further confirmed by the reductive coupling of 4-deoxyglycal **11** with cyclohexanone (Scheme 2). In the absence of a substituent at the C4 position (**11**), the C–C bond at the C3 position in product **12** was formed with no selectivity (isomer ratio of 2:3; Scheme 2).

Table 2: SmI_2-induced umpolung of D-glucal derivatives **7a–e**.[a]



Entry	Substrate		Ketone	Product	Yield [%][b]
1		**7a**	cyclohexanone	**8a**	33[c]
2		**7b**	cyclohexanone	**8b**	63
3		**7c** R = Et	cyclohexanone	**8c**	60
4		**7c**	cyclopentanone	**8d**	56
5		**7c**	cyclobutanone	**8e**	54
6		**7c**	*N*-Boc-piperidin-4-one	**8f**	55
7		**7d** R = Ph	cyclohexanone	**8c**	63
8		**7e**	cyclohexanone	**8g**	56

[a] Reaction conditions: SmI_2 (5 equiv), ketone (3 equiv), THF, 1–2 days at room temperature. [b] Yield after purification by column chromatography on silica gel. [c] Reaction performed at 0 °C for 2 h. Carbohydrate numbering is used.



Scheme 2. SmI_2-induced umpolung of D-galactal derivatives **9a** and **9b** and 4-deoxyglycal **11**. Bn = benzyl, Bz = benzoyl.

This study was completed with coupling reactions of an important glycal that is derived from *N*-acetyl neuraminic

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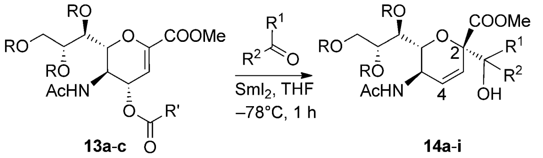
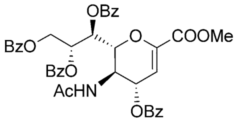
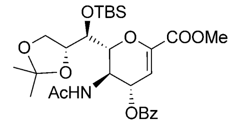
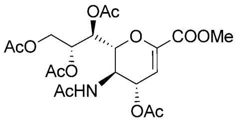
Table 3: SmI_2-induced umpolung of glycals from *N*-acetyl neuraminic acid (Neu5-Ac2en) derivatives **13 a–c**.[a]



Entry	Substrate		Ketone	Product	Yield[b] [%]
1		**13 a**	cyclohexanone	**14 a**	97
2		**13 b**	cyclohexanone	**14 b**	97
3		**13 c**	cyclohexanone	**14 c**	96
4		**13 c**	cyclopentanone	**14 d**	97
5		**13 c**	cyclobutanone	**14 e**	96
6		**13 c**	4-*tert*-butylcyclohexanone	**14 f**	88
7		**13 c**	*N*-Boc-piperidin-4-one	**14 g**	96
8		**13 c**	propanone	**14 h**	92
9		**13 c**	butan-2-none	**14 i**	91[c]

[a] Reaction conditions: SmI_2 (3 equiv), ketone (2 equiv), THF, 1 h, −78 °C. [b] Yield after purification by column chromatography on silica gel. [c] Isolated as a 1:1.2 mixture of diastereomers. TBS = *tert*-butyldimethylsilyl.

acid (Neu5Ac2en). A selective umpolung approach would offer useful modifications of the allylic system in Neu5Ac2en derivatives. With these derivatives, the umpolung reaction with SmI_2 was facile, and after optimization, it was found that the best method was to run the reaction under the Barbier conditions at −78 °C for one hour (Table 3). Under these conditions, the allylic benzoates **13 a** and **13 b**[13] provided exclusively the C2-products **14 a** and **14 b** in 97 % yield each. Readily available peracetylated Neu5Ac2en **13 c**[13,14] was also an excellent substrate and afforded the C2-coupling products **14 c–i** in 88–97 % yield (entries 3–9). The structures of the C2-products **14** were assigned by NMR analysis.[15]

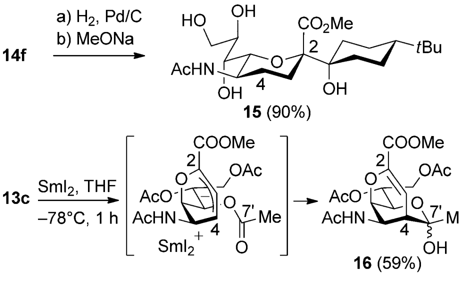
Furthermore, their structures were confirmed by NMR analysis of the reduction product (H_2, Pd/C, AcOEt) of **14 f** after deprotection (**15**, Scheme 3).[13,16] This compound corresponds to a 4-deoxy-α-*C*-glycosyl analogue of *N*-acetyl neuraminic acid.

Without an external ketone, bicyclic derivative **16** was formed in 59 % yield by treating glycal **13 c** with SmI_2 under identical conditions (Scheme 3).[17,18] This intramolecular coupling reaction revealed that the C4 position of the allylic system acts as a nucleophile when no intermolecular coupling partner is available.

The high reactivity of peracetylated **13 c** is remarkable as this compound does not react under palladium catalysis, because the formation of the π-allyl palladium complex is too difficult.[13,19] The reduction of glycals **7 a–e**, which belong to the hexose series, is thought to proceed through a selective electron transfer to the carbonyl group of the allylic moiety, leading to allylic radical **A**, which is further reduced to the allylic samarium derivative **B** (Scheme 4). This explains why allylic benzoates and carbonates are more efficient substrates than acetates (Table 1 and Table 2).

Because of the very different reaction conditions, it is likely that the mechanism for the reduction of Neu5Ac2en derivatives **13** involves a distinct mechanism, which explains the excellent reactivity of peracetylated **13 c**.[20] We suggest that the transformation may start with the formation of radical enolate **C**,[6,21] which is possibly facilitated by chelation of the samarium atom by the endocyclic oxygen atom. This radical is further reduced to the dianionic species **D**, which undergoes elimination to form **E**. Subsequent coupling with the ketone then proceeds with the same α stereoselectivity that was already observed with similar samarium enolates derived from NeuAc derivatives.[22,23] Further work is needed to clarify this point.

In summary, the umpolung of glycals proceeds under simple experimental conditions (SmI_2 in THF) and in a chemoselective fashion in the presence of many other reducible groups (*O*-acyl and NHAc moieties). For the hexose series, the corresponding allyl samarium reagent reacts with ketones at the C3 position with high stereoselectivity, which is controlled by the substituent at the C4 position. For the sialic acid series, the completely regio- and stereoselective coupling process at the anomeric carbon atom provides a new approach to α-*C*-glycosides, which complements our previously described samarium-promoted routes from the anomeric 2-thiopyridyl and acetyl derivatives.[22] Further work to elucidate the mechanism of this transformation and to extend this method to the preparation of modified *C*-sialosides, which are useful for an exploration of their interactions with



Scheme 3. SmI_2-induced intramolecular coupling with peracetylated Neu5Ac2en **13 c**. Reaction conditions: a) H_2, Pd/C (5 %), AcOEt, RT, 24 h; b) MeONa, MeOH, RT.

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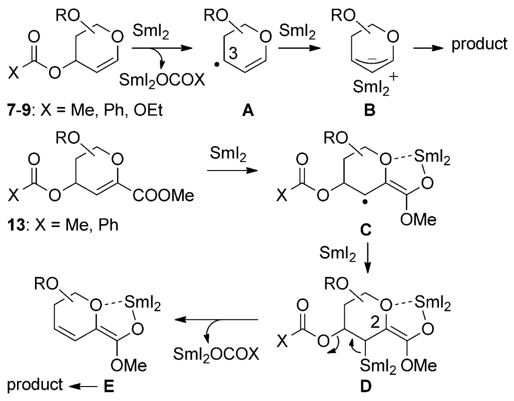

Scheme 4. Proposed mechanism for the SmI$_2$-induced umpolung of hexose glycals **7a–e** and methyl ulosonate glycals **13a–c**.

sialo-binding proteins, is currently underway in our laboratories.

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[16] Diagnostic for the configuration determination of the quaternary center at the C2 position is the large value of the heteronuclear $^{3}J_{\mathrm{C1,H3_{ax}}}$ of 8.1 Hz for **15** in a $_{5}C^{2}$ chair conformation.

[17] The structure of **16** was deduced from its 1D ^{1}H and ^{13}C and 2D (COSY, HSQC, and HMBC) NMR spectra (see the Supporting Information). It is a single compound, but the configuration at the C7′ position has not yet been determined.

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