Enantioselective [1,2]-Stevens Rearrangement Using Sugar-Derived Alkoxides as Chiral Promoters

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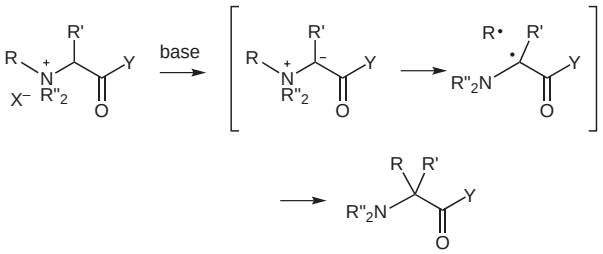
Dedicated to the memory of the late Professor Yoshihiko Ito who passed away on 23 Dec. 2006

Abstract: The first example of enantioselective base-induced [1,2]-Stevens rearrangement was achieved by using the newly developed D-glucose-derived lithium alkoxide as a chiral promoter. This rearrangement provides an α-amino ketone having a pseudoquaternary chiral center in an enantioenriched form.

Key words: asymmetric synthesis, amines, carbohydrates, radical reactions, rearrangements

[1,2]-Stevens rearrangement, which involves an 1,2-alkyl shift from nitrogen to carbon in a quaternary ammonium ylide system, is one of the most classical anionic rearrangements.[1,2] This class of rearrangements has been proposed to proceed via a radical dissociation–recombination mechanism, but not in a concerted fashion (Scheme 1).

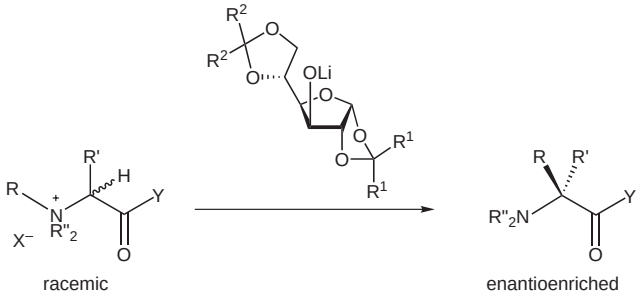


Scheme 1

Despite its long history and significant synthetic potential as a straightforward approach to chiral amines and α-amino ketones, the development of an enantioselective version of the [1,2]-Stevens rearrangement is severely limited, mainly due to its radical mechanism.[2–6]

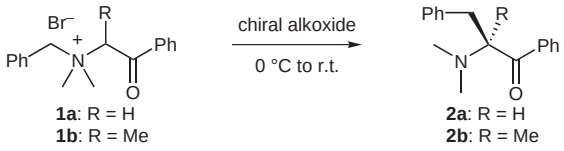
We now disclose an efficient enantioselective approach for the [1,2]-Stevens rearrangement, which has been achieved by the newly developed D-glucose-derived alkoxide protocol (Scheme 2).

One of the characteristic features of the Stevens rearrangement is that the reaction can be promoted by a mild base such as aqueous alkali. Therefore, we have envisaged that a chiral alkoxide would be a suitable chiral promoter for this rearrangement. Our initial efforts were directed to



Scheme 2

the exploration of appropriate chiral alkoxides in the reaction involving the classical Stevens' substrate **1a** (R = H) as a model (Scheme 3).[1,7] The reactions were carried out in a THF solution of **1a** in the presence of excess of easily available chiral alkoxides at 0 °C to room temperature.[8,9] However, all the chiral alkoxides **3**–**6** derived from (*S*)-α-phenethyl alcohol,[10] (*S*)-(–)-1,1′-bi-2-naphthol [(*S*)-BINOL],[11] (–)-borneol,[12] and (–)-norephedrine-derived α-amino alcohol[13] yielded only a racemic **2a** (R = H) in poor yields (Figure 1).[14] At this stage, we suspected the possibility of the racemization of **2a,** and changed the substrate from **1a** to **1b** (R = Me, racemic), which provided **2b** with a pseudoquaternary chiral center.[15,16] Not surprisingly, the reaction of **1b** with excess of **6** in THF at 0 °C afforded **2b** in an optically active form, albeit with low enantiopurity [20% yield, 13% ee (*S*)].[17]



Scheme 3

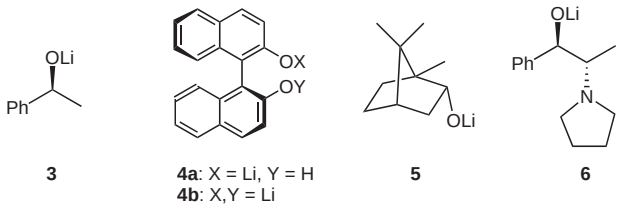


Figure 1

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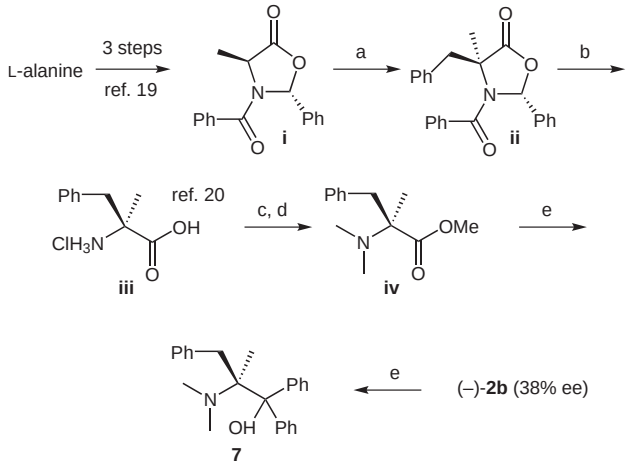
After several attempts using **6**, no significant improvement was observed, except for a slightly better result obtained by changing the solvent from THF to toluene [43% yield, 16% ee (*S*)]. The absolute stereochemistry of the rearrangement product **2b** was determined as *S* by comparing the specific rotation of its alcohol derivative **7** with that of an authentic sample of (*S*)-**7**, which was prepared from L-alanine-derived oxazolidinone via the Seebach and Mutter procedure, as shown in Scheme 4.[18–20]



Scheme 4 *Reagents and conditions*: (a) LHMDS then BnBr, THF–DMPU; (b) concd HCl; (c) $SOCl_2$, MeOH; (d) MeI, K_2CO_3, acetone; (e) PhLi, THF.

As the abovementioned results indicated the possibility of a suitable chiral promoter yielding high enantioselectivity in the reaction providing amino ketones with a stereogenic pseudoquaternary center, we focused our attention on sugar-derived alkoxides for the construction of an appropriate chiral environment in this reaction due to their availability and structural diversity.[21] Accordingly, we first examined a similar reaction of **1b** using the easily available D-glucose-derived lithium alkoxide **8** as a chiral promoter (Figure 2).[22] As we expected, the reaction afforded 24% ee of (*S*)-**2b** in moderate yield (Table 1, entry 1).[23,24] Encouraged by this promising result, we next examined the reaction using a variety of D-glucose-derived lithium alkoxides **9**–**11** having two identical bulky acetal moieties at the 1,2- and 5,6-positions.[25] Among them, the alkoxide **10** with cyclohexylidene acetals greatly improved the result in terms of the reactivity and enantioselectivity (entry 3). The steric congestion due to the acetal moiety in the chiral promoters possibly has an impact on the efficiency of the reaction.

Next, we carried out further optimization of the alkoxide structure by fixing the cyclohexylidene acetal moiety at the 1,2-position. New alkoxides **12b**–**14b** were prepared from D-glucose in four steps, as shown in Scheme 5.

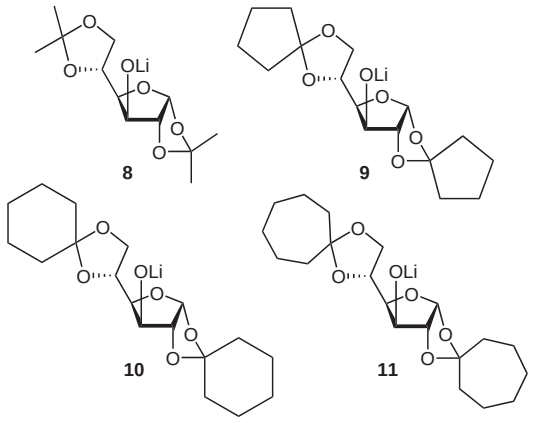


Figure 2

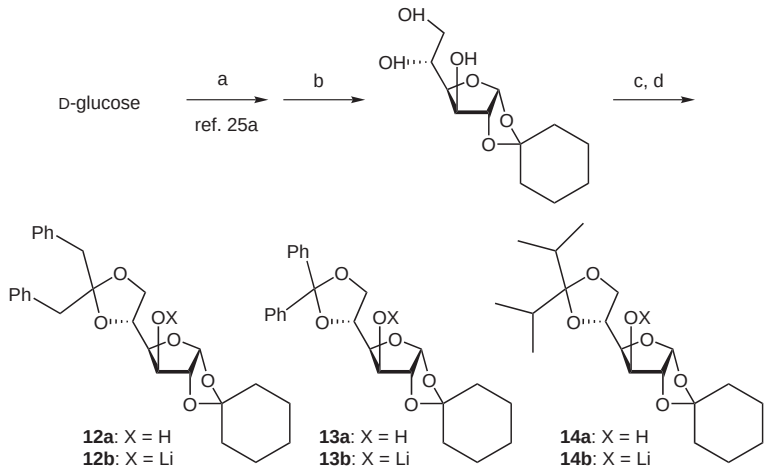
Table 1 [1,2]-Stevens Rearrangement of **1b** using Sugar-Derived Lithium Alkoxide **8**–**14b**[a]

Entry	Alkoxide	Yield of **2b** (%)[b]	ee (%)[c]
1	**8**	57	24 (*S*)
2	**9**	60	19 (*S*)
3	**10**	77	38 (*S*)
4	**11**	46	30 (*S*)
5	**12b**	49	45 (*S*)
6	**13b**	50	4 (*R*)
7	**14b**	91	61 (*S*)

[a] All the reactions were conducted in toluene solution with alkoxide (10 equiv) at 0 °C, followed by warming to r.t.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis using a chiral stationary column (see ref. 14).

Among the differently protected D-glucose-derived lithium alkoxides examined, **14b** with 1,2-cyclohexylidene and 5,6-diisopropylmethyl groups gave the best results (91% yield, 61% ee: entry 7).[26] It is noteworthy that the chiral promoters were easily recoverable from the reaction mixture almost quantitatively (>95%) and reusable. The exact mechanism of the asymmetric induction in the rearrangement step is unclear at present; a more detailed study is required.

In summary, we have described the effectiveness of sugar-derived alkoxides as chiral promoters for the enantioselective [1,2]-Stevens rearrangement. This reaction provides enantioenriched amines having a pseudoquaternary chiral center, which are otherwise difficult to obtain. Thus, this work opens a new chapter in the classical Stevens chemistry and demonstrates a novel facet of an ordinary sugar-derived acetal as an efficient chiral promoter. Further work is in progress to strengthen the synthetic potential of asymmetric Stevens rearrangement as well as the synthetic utility of sugar-derived alkoxides.



Scheme 5 *Reagents and conditions*: (a) cyclohexanone, cat. H_2SO_4, r.t., 29%; (b) AcOH–H_2O (2:1), r.t., 65%; (c) corresponding ketone, trimethyl formate, cat. TsOH, r.t. to 60 °C, **12a**: 65%, **13a**: 68%, **14a**: 81%; (d) *n*-BuLi, toluene, 0 °C.

Acknowledgment

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(7) All the ammonium salts were prepared from the corresponding α-amino ketones and alkyl bromides and purified by recrystallization.

(8) Alkoxides were prepared from the corresponding alcohols using *n*-BuLi (1 equiv) at 0 °C.

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(14) HPLC analysis was carried out on a Chiralcel OD-H column (0.46 × 25 cm) using hexane–*i*-PrOH (150:1; 0.5 mL/min) as the mobile phase.

(15) A rapid racemization of a similar chiral α-amino ketone under weakly basic conditions had been observed; see ref. 5e.

(16) All the compounds were characterized by ^1H and ^{13}C NMR analyses. Data for selected products are as follows. **1b**: ^1H NMR (300 MHz, $CDCl_3$): = 8.48 (d, *J* = 7.5 Hz, 2 H), 7.50–7.70 (m, 8 H), 6.88 (q, *J* = 7.2 Hz, 1 H), 5.29 (d, *J* = 12.0 Hz, 1 H), 5.06 (d, *J* = 12.0 Hz, 1 H), 3.42 (s, 3 H), 3.34 (s, 3 H),

1.79 (d, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): = 196.8, 135.4, 134.0, 133.6, 131.0, 129.9, 129.5, 129.3, 126.7, 69.4, 66.5, 48.1, 47.0, 14.1. **2b**: ^{1}H NMR (300 MHz, $CDCl_3$): = 8.46 (d, *J* = 6.9 Hz, 2 H), 6.90–7.50 (m, 8 H), 3.46 (d, *J* = 12.3 Hz, 1 H), 2.96 (d, *J* = 12.3 Hz, 1 H), 2.36 (s, 6 H), 1.18 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.1, 137.7, 137.6, 132.5, 130.9, 130.5, 128.3, 128.1, 126.5, 72.2, 41.2, 39.0, 14.5. **14**: ^{1}H NMR (300 MHz, acetone-d_6): = 5.83 (d, *J* = 3.6 Hz, 1 H), 4.48 (d, *J* = 3.6 Hz, 1 H), 4.38 (ddd, *J* = 6.6, 6.6, 8.4 Hz, 1 H), 4.16 (d, *J* = 2.7 Hz, 1 H), 4.12 (dd, *J* = 2.7, 6.6 Hz, 1 H), 4.10 (dd, *J* = 6.6, 8.1 Hz, 1 H), 3.80 (dd, *J* = 8.1, 8.4 Hz, 1 H), 2.82 (s, 1 H), 1.90–2.10 (m, 2 H), 1.40–1.60 (m, 10 H), 0.90 (s, 3 H), 0.90 (s, 3 H), 0.88 (s, 3 H), 0.87 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): = 117.2, 112.7, 105.2, 84.6, 82.1, 75.6, 75.0, 71.2, 36.4, 35.6, 34.4, 33.7, 24.8, 23.8, 23.4, 17.4, 17.2.

(17) Similar reactions using alkoxides **3**–**5** afforded racemic **2b** in 16–29% yields.

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(20) Absolute stereochemistry of **iii** was confirmed by the comparison of the specific rotation of its free amine with the reported value. See: Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337.

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(23) Significant countercation-effect for enantioselectivity was observed, i.e., the reaction using the corresponding K or Na alkoxide of **8** afforded only the racemic **2b** in moderate yields.

(24) The enantioselectivity significantly decreased (18% ee), when one equivalent of **8** was used.

(25) The corresponding alcohols of **10**, **11**, and **13** have been reported: (a) For **10**, see: Einhorn, C.; Luche, J. *Carbohydr. Res.* **1986**, *155*, 258. (b) For **11**, see: Luboradzki, R.; Pakulski, Z.; Sartowska, B. *Tetrahedron* **2005**, *61*, 10122. (c) For **13**, see: Mereyala, H. B.; Kodyry, S. R.; Cheemalapati, V. N. *Tetrahedron: Asymmetry* **2006**, *17*, 259.

(26) **Typical Experimental Procedure**: To a solution of 1,2-*O*-cyclohexylidene-5,6-*O*-(diisopropyl)methylidene-α-D-glucofuranose (**14a**; 104 mg, 0.29 mmol) in anhyd toluene (2 mL), was added a solution of *n*-BuLi (0.21 mL of 1.37 M solution in hexane, 0.29 mmol) at 0 °C. After stirring for 30 min at that temperature, benzyldimethyl(α-methylphenacyl)ammonium bromide (**1b**; 10.0 mg, 0.029 mmol) was added. Then, the temperature of the resulting solution was allowed to rise to r.t. and the mixture was stirred for 8 h. The reaction was quenched with pH 7 phosphate buffer, and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography to afford the α-amino ketone (*S*)-**2b** (7.0 mg, 91%, 61% ee) and recovered **14a** (103 mg, 99%).