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LETTERS

Highly diastereoselective reduction and alkylation of (1*R*,2*S*)-*trans*-2-phenylcyclohexanol phenylglyoxylate and pyruvate using hindered hydrides and alkyl aluminates

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Abstract

(1*R*,2*S*)-*trans*-2-Phenylcyclohexanol phenylglyoxylate and pyruvate are reduced with modest to excellent diastereoselectivities (30–99%) by reaction with bulky lithium trialkoxyaluminohydrides and alkylated with excellent diastereoselectivities (88–100%) by addition of hindered lithium alkoxytrialkylaluminates. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Chiral α-hydroxy acid derivatives are important and versatile synthetic intermediates and their synthesis has motivated a great number of studies.[1] In previous reports, we have shown that alkylation and reduction of (–)-menthyl phenylglyoxylate or pyruvate by reaction with hindered lithium alkoxytrialkylaluminates and lithium trialkoxyaluminohydrides provide access to these scaffolds with high diastereoselectivities.[2–5] During this work, we have particularly emphasized the close connection between the steric bulkiness of the reagents and the stereochemical outcome of these reactions. Since the literature reported various easy preparations of both antipodes of *trans*-2-phenylcyclohexanol,[6,7] a powerful substitute[8–10] to 8-phenylmenthol along with its derivatives,[11–13] we here propose the reduction and the alkylation of (1*R*,2*S*)-*trans*-2-phenylcyclohexanol phenylglyoxylate and pyruvate by hindered hydrides and alkyl aluminates (Scheme 1).

In the first part of our work, we studied the influence of the bulkiness of the reducing agents and the temperature on the stereoselectivity in the reduction of chiral ketoesters **1** and **2**. The obtained results are summarized in Table 1.

As expected, by reacting ketoester **1** with more hindered agents, a sharp improvement in the diastereoselectivity was observed (entries 1 and 2). An additional enhancement was also obtained by repeating the reduction with the most hindered hydride **6** at a lower temperature. In this case, a diastereoisomeric excess of 99% was measured (entry 3). When ketoester **2** was subjected to similar reaction conditions,

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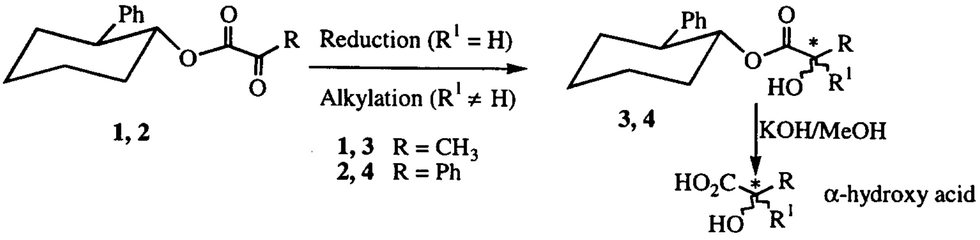
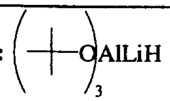
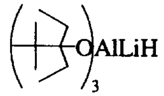
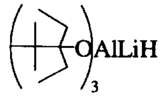
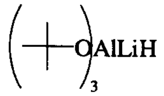
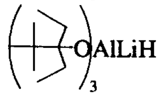
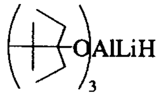
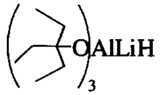
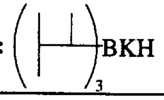


Scheme 1.

Table 1
Reductions of ketoesters **1** and **2** by lithium trialkoxyaluminohydrides[14]

Entry	Ketoesters	Hydrides	Temperature.[a] (°C)	Yield (%)	d.e.[b] (%)	Abs.[c] Conf.
1	**1**	**5** : 	0	79	68	*R*
2	**1**	**6** : 	0	83	94	*R*
3	**1**	**6** : 	-78	80	99	*R*
4	**2**	**5** : 	0	92	30	*R*
5	**2**	**6** : 	0	57	38	*R*
6	**2**	**6** : 	-78	90	40	*R*
7	**2**	**7** : 	-78	90	56	*R*
8	**2**	**8** : 	-78	53	40	*R*

[a] the reactions were performed in THF with 1.25 equiv. of hydride, hydrolyzed by 1M HCl and extracted with Et_2O. Compounds **3** and **4** were obtained as colorless oils.

[b] the d.e. of adducts were determined by GC on a Carbowax column (l = 25m, T = 220 °C)

[c] the absolute configurations of hydroxy esters **3** and **4** were determined by comparison of the retention times with the references obtained respectively from esterification of (*S*)-lactic acid and (*R*)-mandelic acid with trans-2-phenylcyclohexanol.

only moderate diastereoselectivities were determined (entries 4–7). Nevertheless, as previously observed with ketoester **1**, a better result was obtained by: (i) increasing the size of the reducing agent (entries 4, 5 and 7); and (ii) lowering the temperature from 0 to –78°C (entries 5 and 6). As reported in entry 8, the use of the highly hindered trisiamyl borohydride **8** gave the same diastereoselectivity. By considering a transition state in which the chelation of the two carbonyls groups by Li^+ (or K^+) and the steric demand

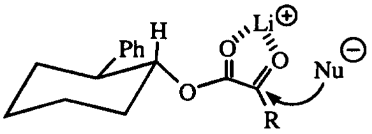
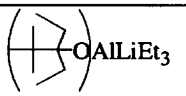


Figure 1.

Table 2
Alkylations of ketoesters **1** and **2** by lithium alkoxytrialkylaluminates[3]

Entry	Ketoesters	Aluminates	Temperature[a] (°C)	Yield (%)	d.e.[b] (%)	Abs.[c] Conf.
1	**1**	**10**	rt	83	98	*S*
2	**1**	**10**	0	82	100	*S*
3	**2**	**10**	0	97	100	*R*
4	**2**	**9**	0	96	88	*R*
5	**2**	**9**	-50	99	91	*R*
6	**2**	**9**	-78	92	89	*R*

9 :


10 :


a) the reactions were performed in hexanes/cyclohexane with 1.25 equivalents of aluminate, hydrolyzed by 1M HCl and extracted with Et_2O. Compounds **3** and **4** were obtained as colorless oils.

b) the d.e. of adducts were determined by GC on a Carbowax column (l = 25m, T = 240 °C)

c) the absolute configurations of hydroxy esters **3** and **4** were determined by the sign of the optical rotation of the corresponding α-hydroxy acids obtained after saponification of esters.[5,15]

of the phenyl group at the 1-position of the *trans*-2-phenylcyclohexanol direct the face stereoselectivity, the major *R*-diastereoisomer, is always obtained as predicted by Whitesell (Fig. 1).[16]

Since the reducing agent derived from 3-ethyl-2,2-dimethyl-3-pentanol allowed good selectivities with both ketoesters **1** and **2**, the same alcohol was used for the preparation of lithium alkoxytrimethyl and triethyl aluminates **9** and **10** and their further condensation with **1** and **2** (Table 2).

As suggested in entries 1 and 4, the nature of the radical alkyl did not play a key role in the stereochemical outcome of the reaction. Thus, condensation of *trans*-2-phenylcyclohexanol phenylglyoxylate with both aluminates **9** and **10** gave the expected ketoalcohols with excellent diastereoselectivities. However, addition of the methyl derivative resulted in only 88% d.e. (entry 4) as compared with the complete induction obtained with the triethylaluminate **10** (entry 3). Therefore, attempts to ameliorate the stereoselectivity of the condensation with aluminates **9** were performed by variations of the temperature (entries 4–6). As reported for entries 5 and 6, only slight improvements were observed by lowering the temperature from 0 to −50 or −78°C, and a 91% d.e. was obtained as the best result. Similarly, condensation of aluminate **10** with ketoester **1** also gave excellent diastereoselectivities (entries 1 and 2). A 98% d.e. was indeed obtained by performing the reaction at room temperature while repeating the condensation at 0°C resulted in a complete induction.

In conclusion, the reaction of lithium trialkoxy alumino hydrides with **1** and **2** afforded α-hydroxy esters with fair to excellent diastereoselectivities. We have shown that improvement of the selectivity was obtained by increasing the steric bulkiness of the reagents. Chiral α-hydroxy esters were also prepared by alkylation with hindered aluminates. In all cases, excellent to complete stereoselectivities were obtained. These results have been favorably compared to those obtained with (−)-menthyl as the chiral auxiliary.

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