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Very High Diastereofacial Stereoselectivity in the α-Methoxy Organolead–Aldehyde Condensation. Stereocontrol of Three Contiguous Chiral Centres

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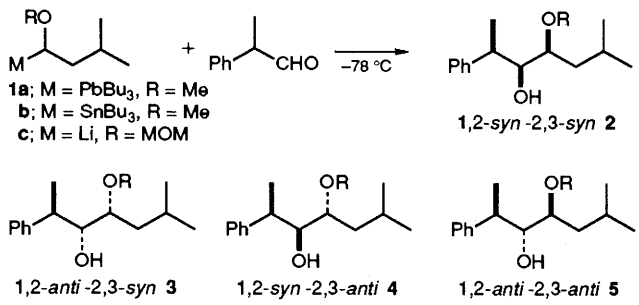
The reaction of the α-methoxylead derivative **1a** with 2-phenylpropanal in the presence of $TiCl_4$ gave the 1,2-*syn*-2,3-*syn* product **2** with very high diastereoselectivity: 1,2-*syn*/1,2-*anti* = 95/5 and 2,3-*syn*/2,3-*anti* = 100/0.

α-Alkoxy organometallic compounds are useful reagents for the synthesis of 1,2-diol derivatives.[1] Recently it has been reported from our laboratory that the Lewis acid mediated reaction of α-alkoxy organolead compounds with aldehydes produces 1,2-diol derivatives in a stereodivergent way by merely changing the Lewis acid: $TiCl_4$ gives *syn*-diols whereas $BF_3{\cdot}OEt_2$ affords *anti*-diols.[2] If there is a chiral centre at the α-position of the aldehyde and if the reaction of these aldehydes with α-alkoxy-lead compounds proceeds with high diastereofacial stereoselectivity, we should be able to control the stereochemistry of three contiguous chiral centres including a diol unit. Such a chiral component is often encountered in the synthesis of certain natural products. We report that very high diastereofacial stereoselectivity is accomplished by the use of the α-methoxy-organolead **1a**, whereas the use of other α-alkoxy organometallic compounds results in low stereocontrol or in low chemical yield.

We examined the reaction of (±)-2-phenylpropanal with some α-alkoxy organometallic compounds **1** (± form). The results are summarized in Table 1. The lithium reagent **1c** produced high 1,2-*syn* selectivity, but virtually no 2,3-*syn*/2,3-*anti* selectivity was observed. The tin reagent **1b** gave significantly high 1,2-*syn*- and extremely high 2,3-*syn*-selectivity, but the chemical yield was disappointing. Very high 1,2-*syn*- and 2,3-*syn*-selectivity and a good chemical yield were accomplished with the $TiCl_4$-mediated reaction of the lead reagent **1a**. The reactivity of **1b** towards the aldehyde is possibly lower than that of **1a**, and therefore most of the reagent **1b** would be decomposed in the presence of $TiCl_4$ prior to the reaction with the aldehyde. The high 2,3-*syn*-selectivity is consistent with the use of $TiCl_4$ as a Lewis acid.[2] The very high 1,2-*syn* selectivity from 2-phenylpropanal is noteworthy,[3] since it is not easy to achieve such a high selectivity in nucleophilic additions to this aldehyde.[4] We also examined the reaction of **1a** with 2-methylbutanal or 3-phenylbutanal, but low diastereofacial selection was obtained. In the former case there is not such a large steric and stereoelectronic difference between the two substituents (Me and Et) at the α-position of the aldehyde, and in the latter case the stereogenic centre is at the β-position.



1a; M = $PbBu_3$, R = Me
b; M = $SnBu_3$, R = Me
c; M = Li, R = MOM

1,2-*syn*-2,3-*syn* 2

1,2-*anti*-2,3-*syn* 3 **1,2-*syn*-2,3-*anti* 4** **1,2-*anti*-2,3-*anti* 5**

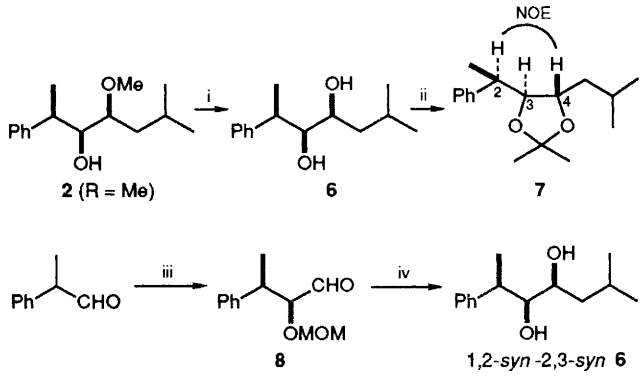
The relative stereochemistry of the products was determined by independent synthesis of authentic material or by ^1H NMR analyses of the cyclic compounds derived from them.† The 1,2-*syn*-2,3-*syn*-**2** (R = Me) was converted to the diol **6** upon treatment with Ac_2O–pyridine, $AlCl_3$–EtSH[5] and KOH–MeOH; acetylation of the free OH, demethylation and

Table 1 Reactions of **1** with 2-phenylpropanal[a]

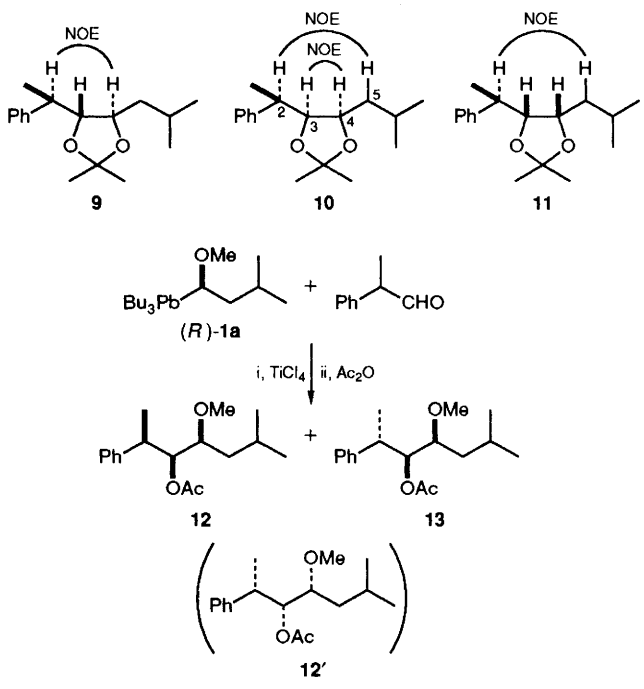
	Lewis acid	Isolated yield of products (%)	Ratio of stereoisomers **2**:**3**:**4**:**5**	1,2-*syn*/1,2-*anti*	2,3-*syn*/2,3-*anti*
1a	$TiCl_4$	74	95:5:—:—	95/5	100/0
1b	$TiCl_4$	19	90:10:—:—	90/10	100/0
1c	—	81	49:4:43:4	92/8	53/47

[a] To a CH_2Cl_2 solution of the aldehyde and $TiCl_4$ (1:1) at −78 °C was added 0.5 equiv. of **1a**. The diastereoisomer ratio was determined by 270 MHz ^1H NMR spectroscopy.

† ^1H NMR (270 MHz) data (δ in $CDCl_3$): **2** (R = H), 7.33–7.20 (5H, m), 3.49–3.45 (2H, m), 2.96 (C-2-H, dq, *J* 7.0 and 7.0 Hz), 1.95 (2H, brs, $w_{1/2}$ 16 Hz), 1.70 (1H, m), 1.42–1.27 (2H, m), 1.35 (3H, *J* 7.0 Hz), 0.83 (3H, d, *J* 6.6 Hz) and 0.82 (3H, d, *J* 6.6 Hz); HRMS (EI), calc. for $C_{14}H_{22}O_2$ 222.1620, found *m/z* 222.1620. **3** (R = H) 7.37–7.22 (5H, m), 3.69 (C-4-H, ddd, *J* 9.2, 4.0 and 2.9 Hz), 3.48 (C-3-H, dd, *J* 7.3 and 2.9 Hz), 3.00 (C-2-H, dq, *J* 7.3 and 7.0 Hz), 1.84–1.69 (3H, m), 1.55 (1H, ddd, *J* 13.9, 9.2 and 5.5 Hz), 1.34 (1H, m), 1.33 (3H, d, *J* 7.0 Hz), 0.95 (3H, d, *J* 6.6 Hz) and 0.90 (3H, d, *J* 6.6 Hz); IR ν(CCl_4)/cm^{-1} 3600–3200, 2950, 1495, 1450 and 1380. **4** (R = H) 7.32–7.18 (5H, m), 3.77 (C-3-H, dd, *J* 8.5 and 4.0 Hz), 3.43 (C-4-H, m), 2.85 (C-2-H, ddq, *J* 7.0, 1.0 and 7.0 Hz), 1.68 (1H, m), 1.50–1.26 (4H, m), 1.38 (3H, d, *J* 7.0 Hz), 0.92 (3H, d, *J* 6.5 Hz) and 0.69 (3H, d, *J* 6.5 Hz); IR ν(CCl_4)/cm^{-1} 3600–3200, 2955, 1500, 1470, 1460, 1060, 1010 and 705. HRMS (EI), calc. for $C_{14}H_{22}O_2$ 222.1620, found *m/z* 222.1622. **5** (R = H) 7.37–7.22 (5H, m), 3.80–3.73 (2H, m), 2.85 (C-2-H, dq, *J* 7.0 and 7.0 Hz), 1.87 (1H, m), 1.76 (1H, d, *J* Hz), 1.60 (1H, d, *J*, Hz), 1.57 (1H, m), 1.29 (1H, m), 1.24 (3H, d, *J* 7.0 Hz), 1.00 (3H, d, *J* 7.0 Hz) and 0.94 (3H, d, *J* 6.5 Hz); IR ν(CCl_4)/cm^{-1} 3600–3300, 2970, 1500, 1460, 1385, 1040 and 705. HRMS (EI), Calc. for $C_{14}H_{22}O_2$ 222.1620, found *m/z* 222.1622.



Scheme 1 *Reagents and conditions*: i, Ac_2O, pyridine, then $AlCl_3$, EtSH, then KOH, MeOH; ii, $(MeO)_2CMe$; iii, $Li^+[SCH_2CH_2CH_2SCH]^-$, then MOMCl ($MeOCH_2Cl$), then HgO, BF_3; iv, $BrMgPr^i$, then H^+.



hydrolysis gave **6** in 51% yield. Normal acetonide formation with 2,2-dimethoxypropane gave **7** in 83% yield. Positive NOEs between 2-H and 4-H were observed; NOEs between 2-H and 3-H were not detected. Accordingly, the stereochemistry of the two hydroxy groups must be *syn* as shown in **6**. The addition of 1,3-dithianyllithium to 2-phenylpropanal gave the 1,2-*syn* alcohol‡ in 78% yield, which was converted to the methoxymethyl (MOM) protected derivative in 94% yield. Removal of thioacetal protection with $HgO–BF_3·OEt_2$ gave **8** in 64% yield (*syn*/*anti* = 19/1). Chelation-controlled addition[6] of isobutylmagnesium bromide to **8** followed by removal of the MOM protection gave **6** in 76% yield. It is well known that the reaction of Grignard reagents with α-alkoxyaldehydes produces a chelation product with very high diastereoselectivity,[6] and the 1,2-*syn* chelation product derived from **8** was in fact identical with **6** derived from **2**. Similarly, the acetonide **9** was prepared from **3** (R = Me), and the acetonides **10** and **11** were prepared from **4** (R = H) and **5** (R = H), respectively, which were isolated from the reaction of **1c**. NOEs were observed between 2-H and 4-H of **9**, indicating *syn*-stereochemistry. The 1,2-*anti*-stereochemistry of **3** was determined from the reaction of isobutylmagnesium bromide with the minor diastereoisomer (19 : 1) of **8**; 1,2-*anti*-2,3-*syn* chelation, *i.e.* **3** (R = H), was obtained. The 1,2-*syn* and 1,2-*anti* stereochemistry of **4** and **5** was determined by the reaction pattern of **1c**.

Finally we examined the reaction of optically active **1a** (93% enantiomeric excess, e.e.) with racemic 2-phenylpropanal in order to discover whether or not kinetic resolution of the aldehyde takes place. The reaction was carried out with a 1 : 1 ratio of (*R*)-**1a**: aldehyde : $TiCl_4$. Again, the 1,2-*syn*-2,3-*syn* product was obtained with a high level of diastereoselectivity (1,2-*syn*-2,3-*syn*/1,2-*anti*-2,3-*syn* = 95/5) in 46% yield based on the aldehyde. However, the e.e. of the major product was 58%, indicating that not only the normal adduct **12** but also its enantiomer **12′** was produced. The e.e. was determined from the ^1H NMR spectra of the 1,2-*syn*-2,3-*syn* product in the presence of 0.1 equiv. of $Eu(hfc)_3$. Clearly, a partial racemization of (*R*)-**1a** to (*S*)-**1a** takes place prior to the C–C bond formation.§ This result suggests that a combination between a racemic lead reagent and a chiral aldehyde may be suitable for kinetic resolution, and we are investigating such possibility. In conclusion, we are now in a position to accomplish very high diastereofacial stereoselectivity in the reaction of certain aldehydes with α-alkoxy-lead reagents, a diastereoselectivity which cannot be achieved by use of other α-alkoxy organometallic compounds.

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References

1 M = Sn, M. Pereyre, J.-P. Quintard and A. Rahm, *Tin in Organic Synthesis*, Butterworth, London, 1987; J. S. Sawyer, A. Kucerovy, T. L. Macdonald and G. J. McGarvey, *J. Am. Chem. Soc.*, 1988, **110**, 842; M = Li, T. Cohen and J. R. Maty, *J. Am. Chem. Soc.*, 1980, **102**, 6900; T. Cohen and M.-T. Lin, *J. Am. Chem. Soc.*, 1984, **106**, 1130; M = MgX, G. J. and M. McGarvey and M. Kimura, *J. Org. Chem.*, 1982, **47**, 5420; M = CuX, R. J. Linderman and A. Godfrey, *J. Am. Chem. Soc.*, 1990, **110**, 6249.
2 J. Yamada, H. Abe and Y. Yamamoto, *J. Am. Chem. Soc.*, 1990, **112**, 6118.
3 Y. Yamamoto and J. Yamada, *J. Am. Chem. Soc.*, 1990, **109**, 4395.
4 Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, 1985, **107**, 6411.
5 M. Node, K. Nishide, M. Sai, K. Ichikawa, K. Fuji and E. Fjita, *Chem. Lett.*, 1979, 97.
6 For a review see M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 556.

‡ The 1,2-*syn* stereochemistry was not determined by spectroscopic methods but by the reaction pattern. It is known that ordinary nucleophiles including 1,3-dithianyllithium produce predominantly the 1,2-*syn* isomer from 2-phenylpropanal.[4] At the stage of the initial addition the 1,2-*syn*/1,2-*anti* ratio was not clear, but removal of the thioacetal protection revealed that the *syn*/*anti* (Cram/*anti*-Cram) ratio at the stage of **8** was 19/1.

§ No racemization took place in the reaction of (*S*)-α-methoxyethyl-lead with benzaldehyde.[2] The reactivity of 2-phenylpropanal is lower than that of benzaldehyde, and thus the racemization presumably occurs prior to the coupling.