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REAGENT-CONTROLLED ENANTIOSELECTIVE HOMOALDOL REACTION WITH CHIRAL 1-OXYALLYLLITHIUM DERIVATIVES. ENANTIO-DIVERGENT TUNING BY ACHIRAL TITANIUM REAGENTS

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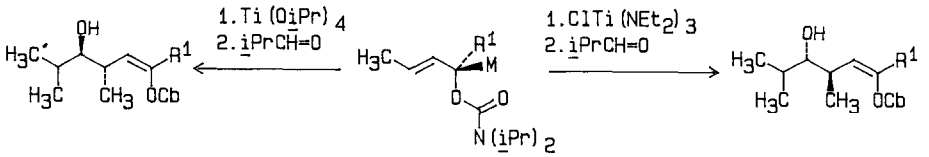
Abstract. Optically active 2-alkenyl carbamates are deprotonated by n-butyllithium with retention of configuration. Lithium titanium exchange by $Ti(OiPr)_4$ proceeds with retention and by $ClTi(NEt_2)_3$ with inversion of configuration. The stereochemical course of addition to aldehydes is mainly determined by the chiral center of the metal allyl reagents to offer a flexible route to both enantiomers of highly substituted ketones.

Recently, we found the first example of a chiral non-racemic allyllithium compound[1] to exhibit considerable configurative stability at the metallated carbon atom; $t_{1/2}$ of racemization for **2b** at -75 °C ≥ 3 h. The optically active carbamate **1b** is lithiated with n-butyllithium/TMEDA with retention of configuration (Scheme 1) and undergoes metal exchange by $ClTi(NEt_2)_3$ with inversion. This was concluded from the opposite stereochemical course of the addition to a prochiral aldehyde[1] which proceeds via a pericyclic process with 1,3-chirality transfer[2] to form Z-anti homoaldol adduct **3b** or ent-**3b**, respectively. The sequence constitutes a novel strategy for reagent-controlled asymmetric homoaldol addition,[3,4] although, due to the low chiral transmission and the low anti-diastereoselectivity for the lithium case, its synthetic value was rather limited at this level.

Scheme 1



3 1 M = H , 2 M = Li·TMEDA ent-3

a $R^1 = CH_3$, b $R^1 = CH_2CH(CH_3)_2$ Cb = C(=O)NiPr$_2$

We now report on useful chiral non-racemic 2-pentanone homoenolate reagents[4] which are obtained conveniently from one enantiomer of (E)-3-penten-2-ol[5] in both enantiomeric forms via the lithium compound **2a** after metal exchange with various achiral titanium reagents.[6]

Carbamate **1a**[7,8] (84% ee) was prepared from (S)-(E)-penten-2-ol.[9] For lithiation,[7] a new inverse procedure was used: To **1a** and n-butyllithium (1.1 eq), mixed below -70 °C in hexane, N,N,N',N'-tetramethyl ethylenediamine (TMEDA, 1.1 eq) is introduced slowly through a syringe and lithiation continued for 2 - 4 h at -78 to -75 °C. Addition of $Ti(OiPr)_4$, $ClTi(NEt_2)_3$ or $ClTi(OiPr)_3$ (1.1 eq, 0.5 h), 2-methylpropanal (1.1 eq, 0.5 h at -75 °C, →20 °C), followed by acidic aqueous work-up, affords a single diastereomer[10] (Z-anti) **3a** and ent-**3a**

of different enantiomeric composition (Scheme 1):
With $Ti(OiPr)_4$, 3.5 h: 59% **3a**, $[\alpha]_D^{20}$ = +4.7, 73% ee,[10] (corr. 87% ee);
with $ClTi(NEt_2)_3$, 4 h: 47% ent-**3a**, $[\alpha]_D^{20}$ = -3.5, 53% ee (corr. 63% ee);
with $ClTi(OiPr)_3$, 4 h: 28% rac-**3a**, $[\alpha]_D^{20}$ = 0.0, 0% ee.
It is evident that the metal exchange takes the opposite stereochemical course with $Ti(OiPr)_4$ (retention) and $ClTi(NEt_2)_3$ (inversion)[1] but is not stereospecific with $ClTi(OiPr)_3$. The configurative stability of the titanium intermediates is surprisingly high. Even, when the solution of **2a**/$Ti(OiPr)_4$ was kept for 0.5 h at 20 °C before aldehyde addition, optically active **3a** (87%, 48% ee, corr. 58% ee) was isolated.
A set of similar experiments was performed applying best metallation conditions (1.1 eq n-BuLi, 4 h) and using (S)- or (R)-(t-butyldimethylsilyloxy)-propanal[11] **4**. As it is seen from Scheme 2 and Table 1, run 1 - 4, the adducts[12,13] **7** or **8**, ent-**8** or ent-**7** are formed via the tentative intermediates[14] **5** or **6**, respectively, with 82 - 90% ds. The accompanying minor diastereomer (10 - 18%) is easily separated by flash chromatography. In part, its formation is caused by the enantiomeric impurity (8%) of the starting material **1a** (84% ee). The remaining amount is the result of a slow racemization of the metallated reagents **2**, **5**, or **6** and of a small positive or negative kinetic resolution.[15]

Scheme 2

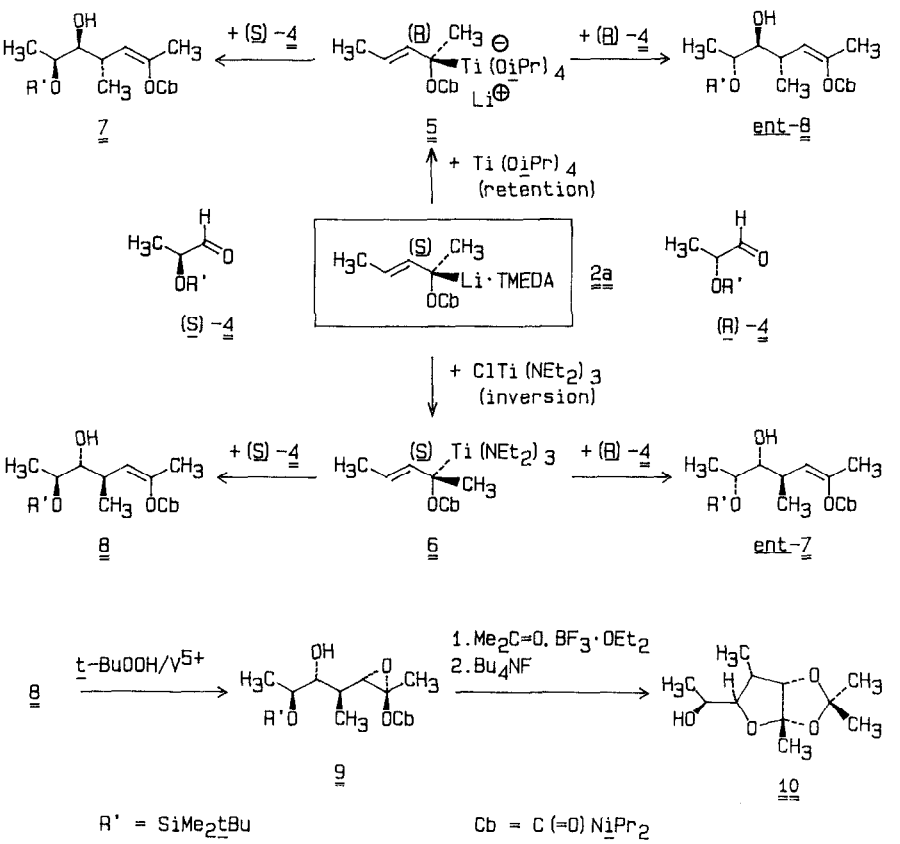


Table 1: Lithiation of **1a** and addition to aldehydes (S)- and (R)-**4** after metal exchange

Run	Reagents	Products	Yield[b] (%)	Ratio[c]	(Ratio)[d]
1	(S)-**1a**[a], (S)-**4**, $Ti(OiPr)_4$	**7** + **8**	61	85 : 15	(93 : 7)
2	(S)-**1a**, (S)-**4**, $ClTi(NEt_2)_3$	**7** + **8**	60	10 : 90	(2 : 98)
3	(S)-**1a**, (R)-**4**, $Ti(OiPr)_4$	ent-**7** + ent-**8**	60	10 : 90	(2 : 98)
4	(S)-**1a**, (R)-**4**, $ClTi(NEt_2)_3$	ent-**7** + ent-**8**	41	82 : 18	(90 : 10)
5	(S)-**1a**, (S)-**4**, $ClTi(OiPr)_3$	**7** + **8**	[g]	53 : 47	-
6	rac-**1a**[e], (S)-**4**, $ClTi(NEt_2)_3$	**7** + **8**	[g]	50 : 50	-
7	rac-**1a**[e], (S)-**4**, $Ti(OiPr)_4$	**7** + **8**	75	47 : 53	-
8	rac-**1a**[f], (S)-**4**, $Ti(OiPr)_4$	**7** + **8**	67	36 : 64	-
9	rac-**1a**[e], rac-**4**, $Ti(OiPr)_4$	rac-**7** + rac-**8**	80[h]	30 : 70	-

[a] (S)-**1a** with 84% ee (S : R = 92 : 8) Was used. [b] Combined yield after LC separation; scale 1 mmol. [c] Ratio was determined by GC and/or isolation. [d] Corrected for (S)-**1** of 100% ee. [e] Ratio rac-**1** : (S)-**4** = 1 : 1. [f] Ratio rac-**1** : (S)-**4** = 2.4 : 1. [g] Not determined. [h] Scale 25 mmol.

From these results one must conclude:

1. The sense and degree of 1,3-chirality transfer and of asymmetric 1,4-induction depends on the achiral titanium compound used for metal exchange.
2. The asymmetric induction caused by the reagent **5** or **6** overrules the inherent 1,2-diastereofacial differentiation of the chiral aldehyde **4**.

The combinations - (S)-**6**[14] and (S)-**4** or (R)-**5**[14] and (R)-**4** - constitute the "matched pairs"[15] and the RS- and SR-pairs the "mismatched" ones. The experiments run 7 versus run 8 or 9 give a simple protocol for the rapid recognition[16] of configuratively stable organometallics even by using the racemates. Compounds **7** or **8** represent masked γ,δ-dihydroxy ketones which rapidly are further functionalized. Epoxidation[17] of **8** (t-BuOOH/V^{5+}) gave the epoxide[18] **9** which affords after treatment with acetone/$BF_3 \cdot OEt_2$ and desilylation (Bu_4NF) a single furanoside[18,19] **10**.

Altogether, homoenolate reagents based on chiral allyl carbamates of type **1**, in the reaction with chiral aldehydes exhibit a high degree of reagent-control. Thus, they permit the convenient stereo-rational preparation of highly functionalized enantiomerically pure ketone derivatives with few steps; up to four new continuous stereo centers are constructed with two steps optionally in each of both enantiomeric configurations starting from reagent **1**.

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REFERENCES AND FOOTNOTES

1. D. Hoppe, T. Krämer, Angew. Chem. **98** (1986) 171; Angew. Chem. Int. Ed. Engl. **25** (1986) 160.
2. R. W. Hoffmann, B. Landmann, Angew. Chem. **96** (1984) 427; Angew. Chem. Int. Ed. Engl. **23** (1984) 437.- Review: R. W. Hoffmann, Chem. Scr. **25** (1985) 53.
3. V. J. Jephcote, A. J. Pratt, E. J. Thomas, J. Chem. Soc. Chem. Commun. **1984**, 800. - H. Roder, G. Helmchen, E.-M. Peters, K. Peters, H.-G. von

Schnering, Angew. Chem. **96** (1984) 895; Angew. Chem. Int. Ed. Engl. **23** (1984) 898.
4. Reviews: D. Hoppe, Angew. Chem. **96** (1984) 930; Angew. Chem. Int. Ed. Engl. **23** (1984) 932; D. Hoppe in M. P. Schneider (Ed.), Enzymes as Catalysts in Organic Synthesis, p. 176, Reidel Publishing Company, Dordrecht 1986.
5. (S)-(E)-Penten-2-ol, 84% ee[9], $[\alpha]_D^{20}$ = -13.5 (c = 1.7, $CHCl_3$), was obtained by resolution of the racemate by the phthalate method: R.H. Hill, R. Soman, S. Sawada, J. Org. Chem. **37** (1972) 3737. The (R)-enantiomer is readily available from the racemate by enzymatic ester hydrolysis; M. P. Schneider, K. Laumen, unpublished results.
6. Reviews: a) M. T. Reetz, Top. Curr. Chem. **106** (1982) 1; b) B. Weidmann, D. Seebach, Angew. Chem. **95** (1983) 12; Angew. Chem. Int. Ed. Engl. **22** (1983) 31; c) D. Seebach, B. Weidmann in R. Scheffold (Ed.), Modern Synthetic Methods 1983, Salle, Frankfurt 1983; d) M. T. Reetz, Organotitanium Reagents in Organic Synthesis, Springer, Berlin 1986.
7. D. Hoppe, R. Hanko, A. Brönneke, F. Lichtenberg, E. van Hülsen, Chem. Ber. **118** (1985) 2822.
8. Carbamate **1a**, 84% ee: $[\alpha]_D^{20}$ = +10.8 (c = 1.9, $CHCl_3$). Its ee value is assumed to be identical with this of the corresponding alcohol.[5,9]
9. We are obliged to Professor W. A. König, Hamburg, and to Professor V. Schurig, Tübingen, for gas chromatographic determinations of enantiomeric purities by their methods. - W. A. König, The Practice of Enantiomer Separation by Capillar Gas Chromatography, Hüthig-Verlag, Heidelberg 1987. - V. Schurig in (J. Morrison, Ed.) Asymmetric Synthesis, Vol. 1, p. 59, Academic Press, New York 1983.
10. **3**: 300 MHz ^{1}H NMR (δ, $CDCl_3$): 4.96 (dd, $J_{2,3}$ = 10.3 Hz, $J_{2,1'}$ = 1.1 Hz, 2-H); 2.46 (ddq, $J_{3,4}$ = 8.5 Hz, $J_{3,3'}$ = 6.8 Hz, 3-H); 3.10 (dd, $J_{4,5}$ = 3.4 Hz, 4-H). The enantiomeric excess was determined by ^{1}H NMR using Eu(hfc)$_3$.
11. (S)-**4**: S. K. Massad, L. D. Hawkins, D. C. Baker, J. Org. Chem. **48** (1983) 5180. (R)-**4**: $[\alpha]_D^{20}$ = +13.5 (neat); was prepared analogously from (R)-isobutyl lactate (yield 55%).
12. R_F (silica gel, ether/pentane, 1:1), **7**: 0.54,**8**: 0.43. $[\alpha]_D^{20}$, **7**: +6.6 (c = 1.18, CH_3OH); **8**: -5.7 (c = 1.25, CH_3OH). - 300 MHz ^{1}H NMR (δ, $CDCl_3$); **7**: 2.53 (ddq, $J_{3,2}$ = 9.9 Hz, $J_{3,4}$ = 4.9 Hz, 3-H); 3.13 (dd, $J_{4,5}$ = 6.1 Hz, 4-H); 3.76 (dq, $J_{5,6}$ = 4.1 Hz, 5-H); 2.82 (m, OH). **8**: 2.39 (ddq, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 8.5 Hz, 3-H); 3.28 (dd, $J_{4,5}$ = 3.3 Hz, 4-H); 3.85 (dq, $J_{5,6}$ = 6.2 Hz, 5-H); 2.66 (m, OH). ^{13}C NMR (δ, $CDCl_3$), **7/8**/: 18.14/17.13/ (3-CH_3); 19.75/16.49/ (C-6); 19.89/20.08/ (1-CH_3); 32.53/33.47/ (C-3); 70.20/69.96/ (C-5); 79.29/78.62 (C-4); 117.95/119.45/ (C-2); 145.09/145.24/ (C-1); 153.14/153.46/ (C=O).
13. For syn/anti assignment see: B. Landmann, R. W. Hoffmann, Chem. Ber. **120** (1987) 331.
14. Note, that the exchange of Li (**2a**) for Ti (**5** or **6**) causes a change of CIP priorities. Hence, an inversion of the descriptor indicates retention of the configuration.
15. Review: S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, Angew. Chem. **97** (1985) 1; Angew. Chem. Int. Ed. Engl. **24** (1985) 1.
16. R. W. Hoffmann, J. Lanz, R. Metternich, G. Tarara, D. Hoppe, manuscript submitted to Angewandte Chemie.
17. D. Hoppe, J. Lüßmann, P. G. Jones, D. Schmidt, G. M. Sheldrick, Tetrahedron Lett. **27** (1986) 3591.
18. **9**: $[\alpha]_D^{20}$ = + 17.5 (c = 1.4, CH_3OH). **10**: $[\alpha]_D^{20}$ = -40.3 (c = 1.8, CH_3OH); yield 11% from **8** (not optimized yet). - 300 MHz ^{1}H NMR (δ, $CDCl_3$): 1.56 (s, 2-CH_3); 3.85 (dd, $J_{4,5}$ = 10.1 Hz, $J_{4,4'}$ = 3.0 Hz, 4-H); 2.15 (dqd, $J_{5,5'}$ = 6.7 Hz, 5-H); 4.26 (d, $J_{6,5}$ = 4.5 Hz, 6-H); 3.97 (qd, J = 6.8 Hz, 4'-H); 1.12 (d, 4'-CH_3); 1.19 (d, 5'-H).
19. D. Hoppe , G. Tarara, M. Wilckens, P. G. Jones, D. Schmidt, J. J. Stezowski, Angew. Chem. **99** (1987), issue 10 or 11, in press.

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