Pure & Appl. Chem., Vol. 62, No. 10, pp. 1999–2006, 1990.
Printed in Great Britain.

Metallated 2-alkenyl carbamates: chiral homoenolate reagents for asymmetric synthesis

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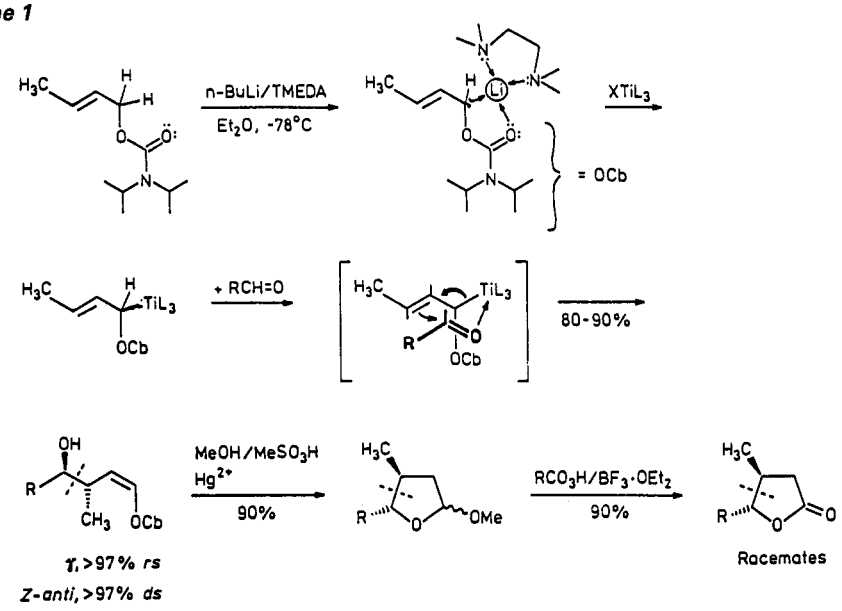
Abstract - Nonracemic chiral 1-lithio-2-alkenyl carbamates are generated by stereospecific deprotonation of optically active 2-alkenyl carbamates, by kinetic resolution with *sec*-butyllithium/(-)-sparteine, or by preferential crystallisation of one of the diastereomeric complexes. After stereospecific lithium titanium exchange, the addition reaction to aldehydes proceeds with a high degree of chirality transfer to yield diastereomerically pure, enantiomerically enriched 4-hydroxy-1-alkenyl carbamates. Some simple transformations giving rapid access to methyl furanosides of methyl-branched 3,6-dideoxy aldohexoses, 4-butanolides and 3-acyl-tetrahydrofuranes are discussed. New reagents for asymmetric nucleophilic alkenoylation (substrate-controlled) or α-(hydroxy)alkylation (reagent-controlled) are introduced.

INTRODUCTION

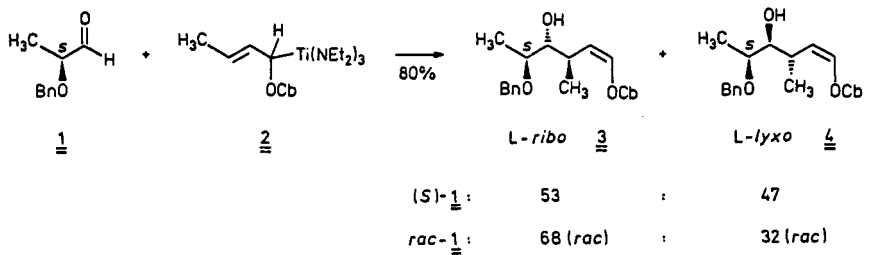
α-Metallated 2-alkenyl *N,N*-diisopropylcarbamates, introduced by us in 1980 (refs. 1-3), were recognized to be valuable homoenolate equivalents. In particular, after exchange of the lithium ion for titanium [TiL_3 = $Ti(OiPr)_3$ or $Ti(NEt_2)_3$] (ref. 4), the carbonyl addition proceeds with high regio- and diastereoselectivity (ref.5). Mercuric acetate catalyzed methanolysis affords γ-lactol ethers, which are oxidized to yield racemic 3,4-*trans*-butanolides (ref. 5). The sequence is outlined in *Scheme 1* for a typical "homoaldol reaction", starting with the (*E*)-2-butenyl carbamate.

Scheme 1



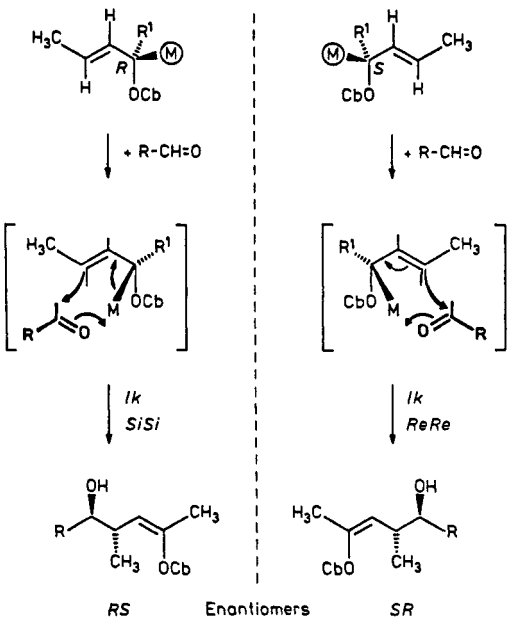
The racemic titanium (*E*)-2-butenyl reagent (L = NEt_2 or O*i*Pr) adds to (*S*)-2-benzyloxypropanal to give both (*Z*)-*anti*-diastereomers with essentially equal amounts (refs. 6-7), but the ratio is changed by double stereodifferentiation (ref. 8-9) when using the racemic pair of reagents (*Scheme 2*). From this, it is deduced that the enantiomerization of the titanium compound is a slow reaction (ref. 8).

Scheme 2



The addition of the carbonyl compound proceeds via a highly ordered chair-like transition state (ref. 10), in which the configuration of the metallo-substituted stereogenic α-carbon atom determines the absolute configuration of the newly created stereocenters (*Scheme 3*). Even, when R represents a chiral residue and, thus, the transition states are diastereomorphous, this fact holds, meaning that α-titanated 2-alkenyl carbamates exhibit a high degree of reagent-controlled stereoselectivity (ref. 11).

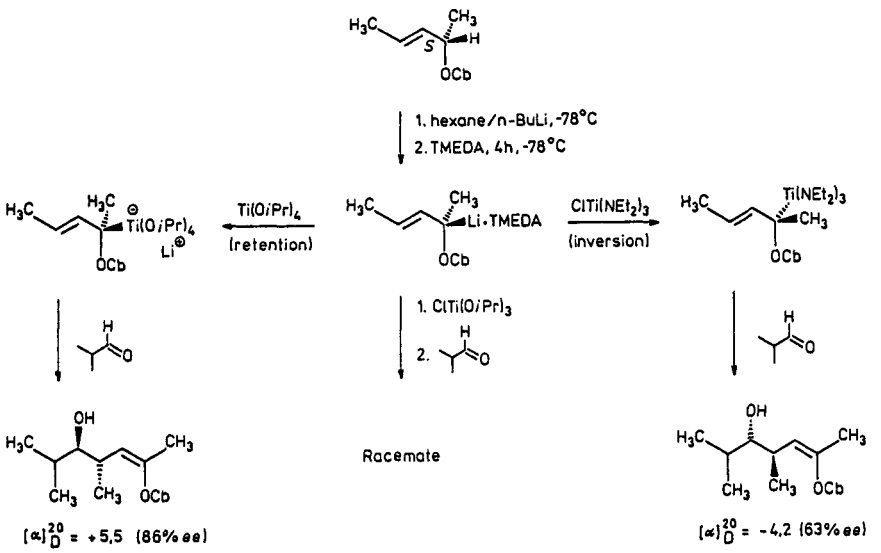
Scheme 3



CONFIGURATIONALLY STABLE CHIRAL 1-METALLO-2-ALKENYL CARBAMATES

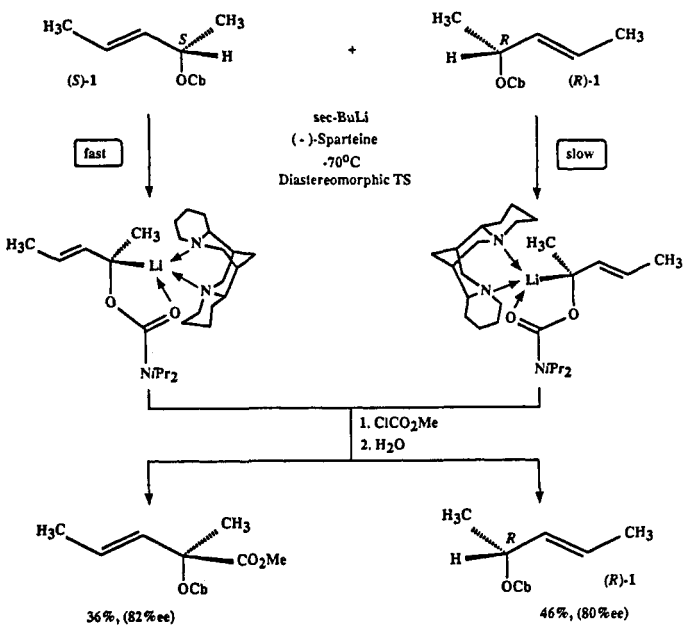
To our great surprise, the (*S*)-3-penten-2-yl carbamate could be deprotonated without loss of the chiral information (*Scheme 4*) (ref. 12). Addition of the lithium compound to 2-methylpropanal furnishes the enantiomerically enriched dextrorotatory 4-hydroxy-1-alkenyl carbamate with low simple diastereoselectivity. It is solely obtained after metal exchange with tetra(isopropoxy)titanium (ref. 13). In contrary, after addition of chloro-tris(diethylamino)titanium, the opposite enantiomer is formed, indicating that the delithiotitanation with both reagents takes different stereochemical courses (*Scheme 4*) (ref. 13). To our best knowledge, the lithium derivatives of secondary carbamates are the first, and up to now, the sole known type of chiral alkali-metal allylic compounds which exhibit preparatively useful configurational stability. The stereochemical divergence of the metal exchange and the high degree of reagent-controlled stereoselectivity was also demonstrated by the reaction with protected (*S*)- and (*R*)-2-oxypropanals (ref. 13).

Scheme 4



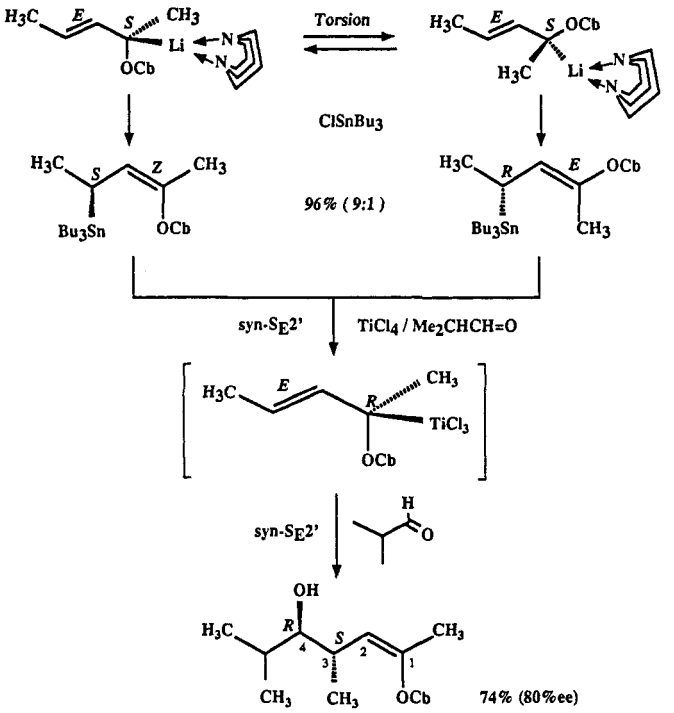
Enantiomerically enriched secondary (*S*)-1-lithio-2-alkenyl carbamates are also formed by enantiomer-differentiating deprotonation by the *sec*-butyllithium/(-)-sparteine complex as shown in *Scheme 5* for the kinetic resolution of the 3-penten-2-yl derivative (ref. 14-15). The (*S*)-carbamate is lithiated rapidly and was trapped by methoxycarbonylation; the (*R*)-enantiomer was recovered unchanged.

Scheme 5



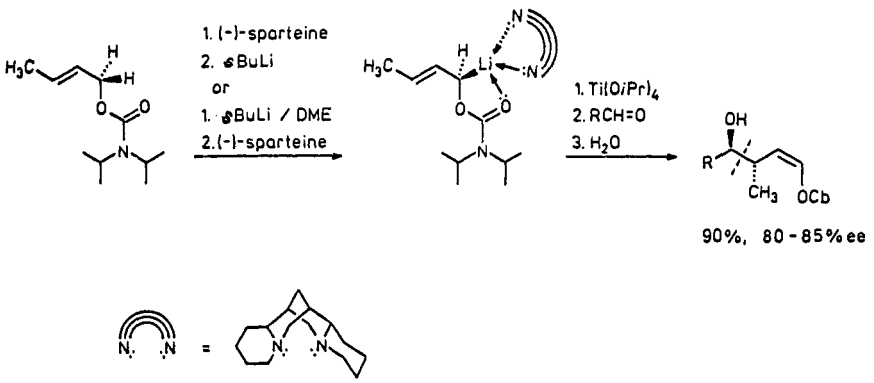
Stannylation of the sparteine complex (ref. 14) (or of the lithium derivatives shown in *Scheme 4*) (refs. 16-17) proceeds γ-selectively and stereospecifically in two competing *syn*-S_E2'-substitution reactions giving rise to a mixture of the (*S,Z*)- and the (*R,E*)-diastereomer (*Scheme 6*). The stannanes are useful stable chiral homoenolate reagents, which develop their reactivity under the influence of Lewis acid (ref. 16). In their reaction with chiral or prochiral aldehydes, the same addition products otherwise obtained after tetra(isopropoxy)titanium exchange from the lithium compound, are formed with high enantiomeric excess. Obviously, the stereo-convergence arises from the stereospecific formation of a stereo-homogeneous α-trichloro-titanium intermediate in a second *syn*-S_E2' process (ref. 18).

Scheme 6



When the deprotonation of the prochiral (*E*)-butenyl carbamate is carried out with *sec*-butyllithium/(-)-sparteine, after lithium titanium exchange, the reaction with aldehydes affords the homoaldol products with 80 - 90% *ee* (*Scheme 7*) (ref. 19). It has been shown that not an enantiotopos-differentiating deprotonation is the origin of enantioselectivity, but a second-order asymmetric transformation. It is caused by preferential crystallization of one of the diastereomeric sparteine complexes which interconvert in solution.

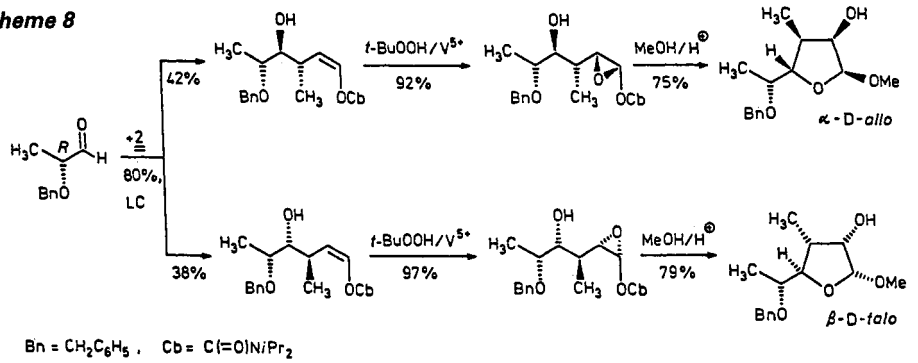
Scheme 7



SYNTHETIC APPLICATIONS

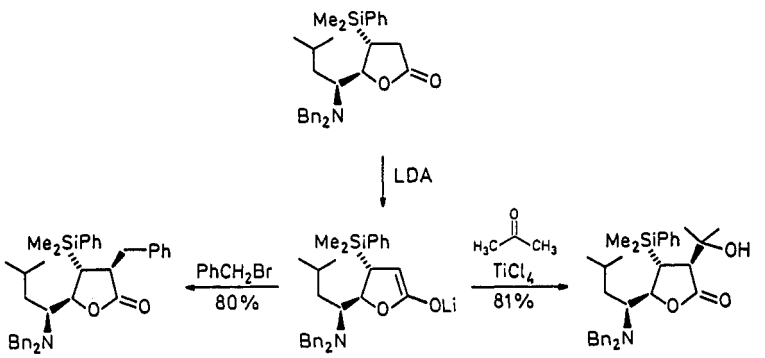
The hydroxyl-directed epoxidation (ref. 20) of the enol carbamates proceeds highly stereoselectively (*Scheme 8*) (refs. 21-22). Acid-catalyzed methanolysis of the epoxides under kinetic control affords the thermodynamically less stable anomers of the methyl furanosides (ref. 13). Inversion of the free 2-hydroxy group leads with few steps to key intermediates (ref. 23) of the *Kinoshita* (ref. 24) Rifamycin S synthesis.

Scheme 8



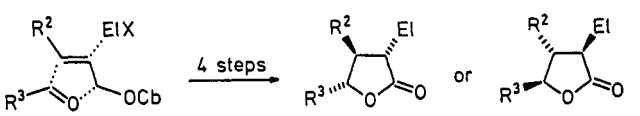
Homochiral *trans*-γ-lactones, obtained by the homoaldol route, are further substituted highly diastereoselectively by means of enolate methodology, as shown in *Scheme 9* (ref. 25).

Scheme 9



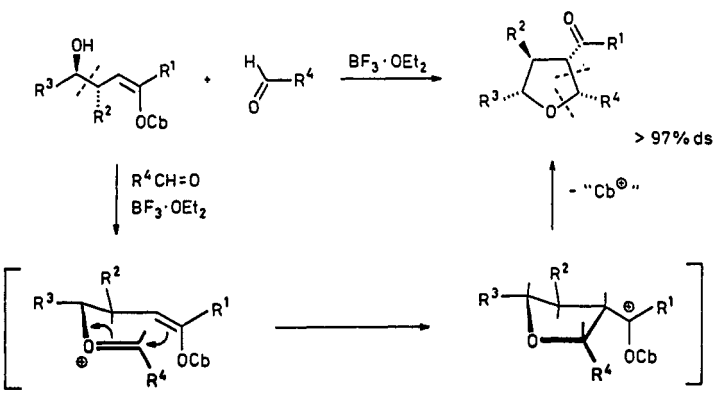
Altogether, a very versatile "brick-box system" is offered for the construction of 2,3,4-*trans*,*trans*-trisubstituted butanolides only in four steps (*Scheme 10*).

Scheme 10



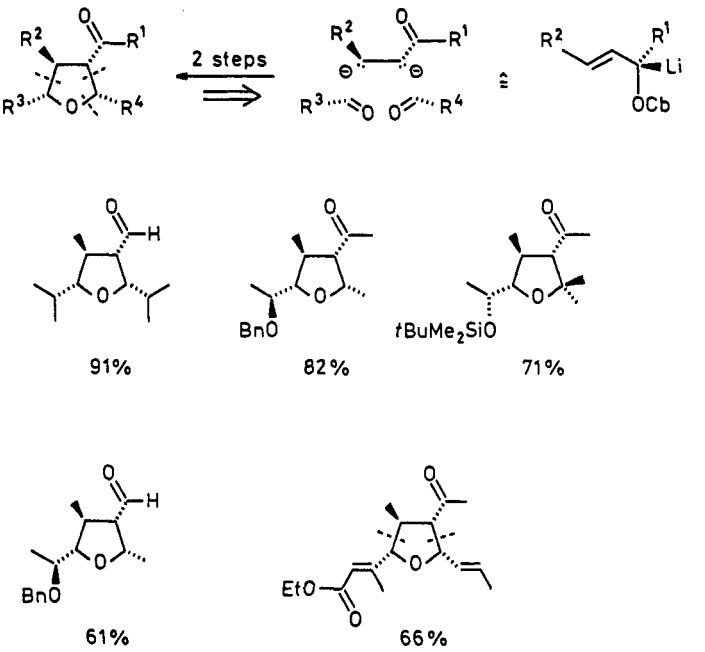
The 1-alkenyl carbamates bear an enol moity of low reactivity. It can be utilized in intramolecular addition reactions via carbenium ion intermediates. The reaction with aldehydes, ketones, or their acetals under boron trifluoride catalysis proceeds smoothly, yielding diastereomerically pure *cis*,*trans*,*trans*-3-acyl-tetrahydrofurans (*Scheme* 11) (ref. 26). The stereochemical outcome is best explained by the cyclization of an (*E*)-oxonium ion via the least sterically crowded transition state.

Scheme 11



Scheme 12 shows some poly-substituted tetrahydrofurans which were obtained by only two reaction steps (refs. 26-27). Here, in the coupled sequence of homoaldol reaction and *Mukaiyama*-type aldol addition, the 1-lithio-2-alkenyl carbamate serves for an equivalent of a chiral α,β-enediolate.

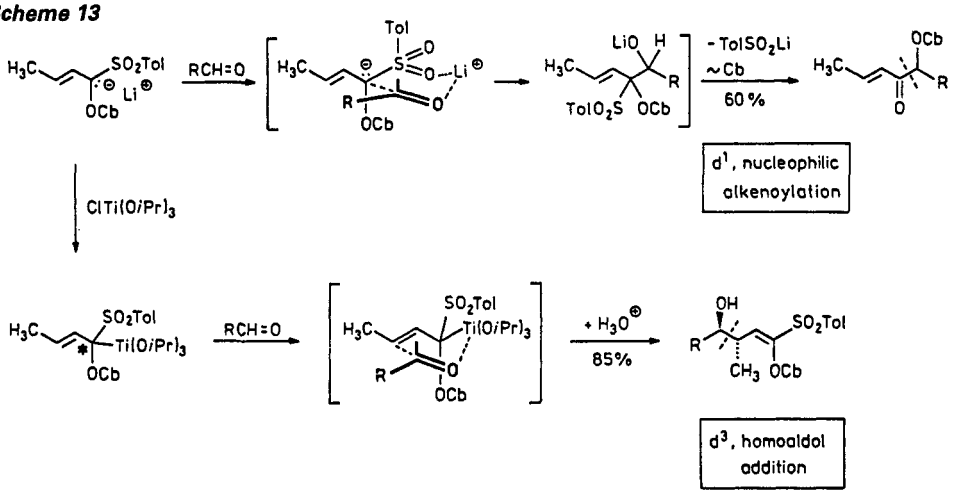
Scheme 12



NUCLEOPHILIC ALKENOYLATION

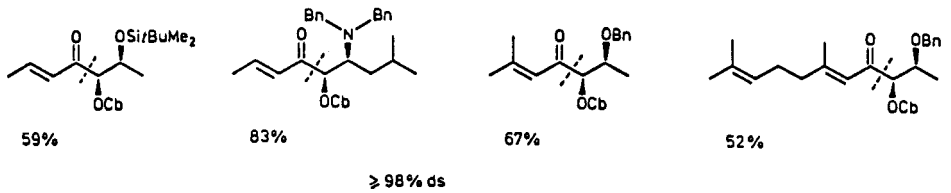
1-Metallated 2-alkenyl carbamates, since these are chiral compounds, exhibit a high degree of reagent-controlled stereoselectivity (refs. 9, 11). Sometimes, the reverse, an asymmetric induction by the chiral substrate onto a prochiral carbanion is desired. We found that the introduction of an electron-withdrawing *p*-toluenesulfonyl group to the 1-lithio-2-alkenyl carbamate causes the necessary configurational lability (*Scheme 13*) (ref. 28). The close contact of the lithium cation to the α-carbon atom is lost and, as a consequence, α-selective carbonyl addition takes place. Migration of the carbamoyl group and elimination of lithium *p*-toluenesulfinate furnishs 2-alkenones. After an irreversible lithium titanium exchange, again, the usual γ-selectivity is observed.

Scheme 13



The nucleophilic alkenoylation of enantiomerically pure aldehydes proceeds with >98% *ds* (ref. 28b). Some examples are collected in *Scheme 14*.

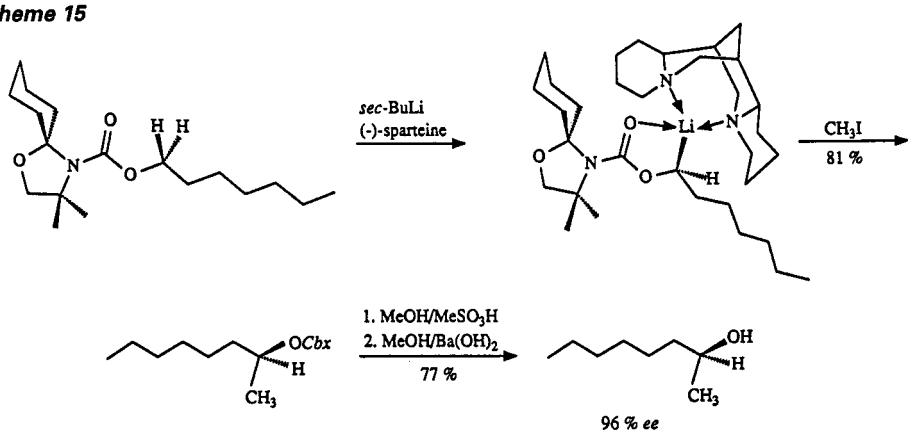
Scheme 14



CONCLUSIONS AND OUTLOOK

Final *Scheme 15* gives a glimpse of very recent exciting developments in α-metallo-carbamate chemistry. When applying a carbamoyl residue, derived from a cyclohexane-spiro-1,3-oxazolidine (ref. 29), which in addition, is later more facile split off than the *N,N*-diisopropylcarbamoyl group, "non-activated" allyl carbamates are readily deprotonated. The application of the *sec*-butyllithium/(-)-sparteine complex achieves an efficient enantiotopos-differentiation to form the configurationally stable lithium (*S*)-α-oxyalkanides (ref. 30). Methylation and, as well, carboxylation, or stannylation proceeds with >95% *ee* (ref. 30). It seems that these are general reactions, because the high enantioselectivity holds for all alkyl carbamates (investigated so far heptyl - as shown in the scheme -, ethyl, butyl, isobutyl ester) (ref. 30). Meanwhile, configurational stability was also detected for certain lithiated 2-alkynyl (ref. 31), benzyl (ref. 32), allenyl (ref. 33), and cyclopropyl (ref. 34) carbamates (ref. 35). Altogether, these novel chiral carbanionic synthons permit the development of new strategies in asymmetric synthesis.

Scheme 15



Acknowledgement One of us (D.H.) wishes to express his best thanks to all of his very skilled coworkers, who were engaged in the project. Generous financial support by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* is gratefully acknowledged.

REFERENCES

1. D. Hoppe, *Angew. Chem.*, *96*, 930-946 (1984); *Angew. Chem. Int. Ed. Engl.*, *23*, 932-948 (1984).
2. D. Hoppe in: *Enzymes as Catalysts in Organic Synthesis*, M.P. Schneider (Ed.), Nato ASI Series C 178, p. 177-198, Reidel Publishing Co., Dordrecht 1986.
3. a) D. Hoppe, R. Hanko and A. Brönneke, *Angew. Chem.*, *92*, 637-639 (1980); *Angew. Chem. Int. Ed. Engl.*, *19*, 625-627 (1980); b) D. Hoppe, R. Hanko, A. Brönneke, F. Lichtenberg and E. van Hülsen, *Chem. Ber.*, *118*, 2822-2851 (1985).

4. a) M.T. Reetz, *Organotitanium Reagents in Organic Synthesis,* Springer Verlag, Berlin 1986; b) D. Seebach and B. Weidmann in: *Modern Synthetic Methods*, R. Scheffold (Ed.), Salle/ Sauerländer, p. 217-353, Frankfurt 1983.
5. a) R. Hanko and D. Hoppe, *Angew. Chem., 94*, 378-379 (1982); *Angew. Chem. Int. Ed. Engl., 21*, 372-373 (1982); b) D. Hoppe and A. Brönneke, *Tetrahedron Lett., 24*, 1687-1690 (1983).
6. D. Hoppe, G. Tarara, M. Wilckens, P.G. Jones, D. Schmidt and J.J. Stezowski, *Angew. Chem., 99*, 1079-1081 (1987); *Angew. Chem. Int. Ed. Engl., 26*, 1034-1036 (1987).
7. D. Hoppe, G. Tarara and M. Wilckens, *Synthesis*, 83-88 (1989).
8. R.W. Hoffmann, J. Lanz, R. Metternich, G. Tarara and D. Hoppe, *Angew. Chem., 99*, 1196-1197 (1987); *Angew. Chem. Int. Ed. Engl., 26*, 1145-1146 (1987).
9. S. Masamune, W. Choy, J.S. Petersen and L.R. Sita, *Angew. Chem., 97*, 1-31 (1985); *Angew. Chem. Int. Ed. Engl., 24*, 1-31 (1985).
10. Y. Li, M.N. Paddon-Row and K.N. Houk, *J. Am. Chem. Soc., 110*, 3684-3686 (1988).
11. R.W. Hoffmann, *Angew. Chem., 99*, 503-517 (1987); *Angew. Chem. Int. Ed. Engl., 26*, 489-503 (1987).
12. D. Hoppe and T. Krämer, *Angew. Chem., 98*, 171-173 (1986); *Angew. Chem. Int. Ed. Engl., 25*, 160-162 (1986).
13. T. Krämer and D. Hoppe, *Tetrahedron Lett., 28*, 5149-5152 (1987).
14. O. Zschage, J.-R. Schwark and D. Hoppe, *Angew. Chem., 102*, 336-337 (1990); *Angew. Chem. Int. Ed. Engl., 29*, 296-297 (1990).
15. For the utilization of organo-lithium/sparteine complexes see: a) H. Nozaki, T. Aratani, T. Toraya and R. Noyori, *Tetrahedron, 27*, 905-913 (1971); b) L.M. Engelhardt, W.P. Leung, C.L. Raston, G. Salem, P. Twist and A.H. White, *J. Chem. Soc., Dalton Trans., 9*, 2403-2409 (1988).
16. T. Krämer, J.-R. Schwark and D. Hoppe, *Tetrahedron Lett., 30*, 7037-7040 (1989).
17. The absolute configuration of the allylstannanes was deduced from the application of the Brewster rule; cf: J.H. Brewster, *Top. Stereochem., 2*, 1-72 (1967).
18. Two subsequent *anti*-S_E2' metal exchanges will furnish the same stereochemical result; cf: J.A. Marshall, B.S. Dehoff and S.L. Crooks, *Tetrahedron Lett., 28*, 527-530 (1987).
19. D. Hoppe and O. Zschage, *Angew. Chem., 101*, 67-68 (1989); *Angew. Chem. Int. Ed. Engl., 28*, 65-66 (1989).
20. K.B. Sharpless, C.H. Behrens, T. Katsuki, A.W.M. Lee, V.S. Martin, M. Takatani, S.M. Viti, F.J. Walker and S.S. Woodard, *Pure Appl. Chem., 55*, 589-604 (1983).
21. D. Hoppe, J. Lüßmann, P.G. Jones, D. Schmidt and G.M. Sheldrick, *Tetrahedron Lett., 27*, 3591-3594 (1986).
22. J. Lüßmann, D. Hoppe, P.G. Jones, C. Fittschen and G.M. Sheldrick, *Tetrahedron Lett., 27*, 3595-3598 (1986).
23. G. Tarara and D. Hoppe, *Synthesis*, 89-92 (1989).
24. M. Nakata, K. Toshima, T. Kai and M. Kinoshita, *Bull. Chem. Soc. Jpn., 58*, 3457-3464 (1985).
25. F. Rehders, unpublished results, University of Kiel, 1989.
26. D. Hoppe, T. Krämer, E. Egert and C. Freire Erdbrügger, *Tetrahedron Lett., 30*, 1233-1236 (1989).
27. B. Jebens, *Diploma Thesis,* University of Kiel, 1989.
28. a)M. Reggelin, P. Tebben and D. Hoppe, *Tetrahedron Lett., 30*, 2915-2918 (1989); b) P. Tebben, M. Reggelin and D. Hoppe, *Tetrahedron Lett., 30*, 2919-2922 (1989).
29. P. Michon and A. Rassat, *Bull. Soc. Chim. Fr.*, 3561-3567 (1971).
30. D. Hoppe, F. Hintze and P. Tebben, *Angew. Chem.*, manuscript submitted.
31. S. Dreller, *Dissertation*, University of Kiel, 1990.
32. D. Hoppe, A. Carstens and T. Krämer, *Angew. Chem.*, manuscript accepted.
33. D. Hoppe and C. Gonschorrek, *Tetrahedron Lett., 28*, 785-788 (1987).
34. M. Paetow, unpublished results, 1990.
35. For a more detailed review see: D. Hoppe, O. Zschage in: R.W. Hoffmann, K.-H. Dötz (Ed.) *Organometallics in Organic Synthesis, 3* (OSM 4), in press, Vieweg Verlag, Braunschweig 1991.