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Enantioselective synthesis via sparteine-induced asymmetric deprotonation

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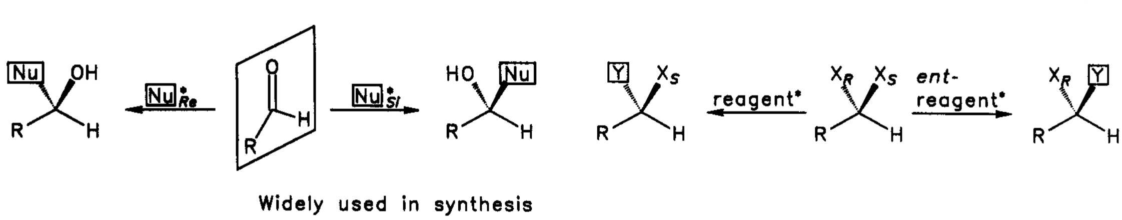
Abstract. The deprotonation of *achiral* alkyl carbamates with *sec*-butyllithium/(-)-sparteine proceeds with a high degree of chiral recognition to form substituted alcohols usually with ≥ 95 % *ee* after reaction with electrophiles followed by deprotection. The stereoselection is kinetically controlled and a qualitative transition state model is proposed. Some studies, concerning the discrimination between both enantiomers of stereogenic alkyl carbamates and on its utilization for the kinetic resolution are reported. The competition between external and internal competition was investigated in few cases. - Finally, we disclose a short report on the enantioselective electrophilic substitution of 1-methylindene; here the origin of stereoselection is an thermodynamically driven epimerization of diastereomeric indenyllithium sparteine complexes.

INTRODUCTION

Many methods for the enantioselective synthesis are based on the selection of a chiral reagent or of a reagent under the influence of a chiral catalyst between the enantiotopic faces of a trigonal carbon moiety. In only a few cases, an efficient selection between enantiotopic groups at a tetragonal carbon atom has been verified (*Scheme 1*).

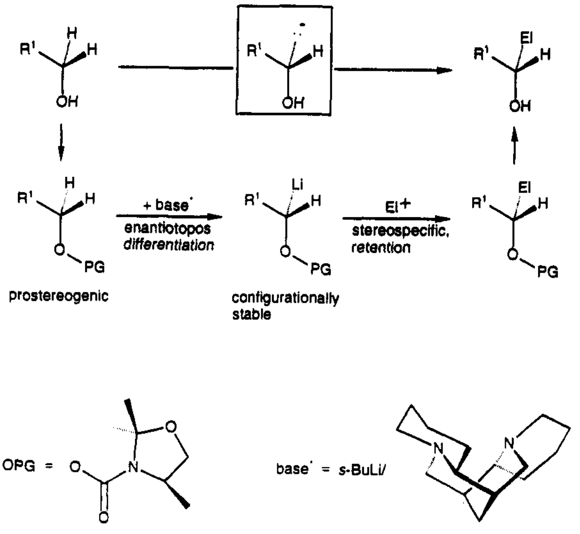
Scheme 1



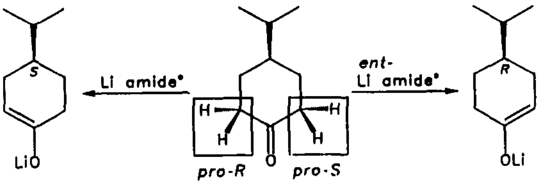
Impressive examples of the latter type have been reported (ref. 1) independently by the research groups of *Koga* and *Simpkins*: 4-Substituted cyclohexanones are deprotonated by chiral lithium amides, derived from simple secondary amines, leading to enantioenriched lithium enolates (*Scheme 2*). Again, the center of reactivity is planar, but the result of the chirality-inducing step is conserved by a remote stereogenic carbon atom.

Based on our studies with chiral lithium carbanions, derived from allyl *N,N*-diisopropylcarbamates, (refs. 2,3), we developed a method which permits the electrophilic substitution of one of the enantiotopic α-protons in an aliphatic alcohol R^1CH_2OH (R^1 = alkyl) via the equivalents of 1-hydroxy-alkanides (ref. 4) (*Scheme 3*): In the first step, the 2,2,4,4-tetramethyloxazolidine-3-carbonyl group (ref. 5) is introduced for the protecting and activating group *PG*. The chiral base, formed from *sec*-butyllithium and (-)-sparteine, removes preferentially the pro-*S* proton, leading to a configurationally stable lithium carbanion (ref. 6). It is attacked by most electrophiles with stereoretention. Finally, the removal of the carbamate group leads to the substituted alcohol with high enantiomeric excess (*ee*):

Scheme 2

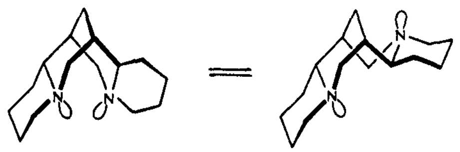


Scheme 3



K. Koga; N.S. Simpkins (1986)

Scheme 4

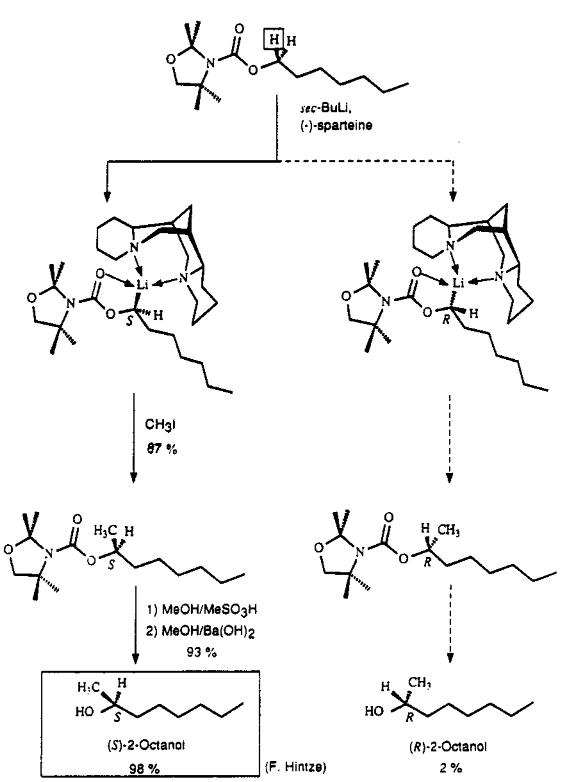


The alkaloid (-)-sparteine is readily available from bitter lupine seed and it is easily recovered due to its low solubility in water. Although it barely misses the C_2-symmetry it is ideally suited for acting as a bidentate ligand for aminophilic cations (ref. 7) (*Scheme 4*). In 1968 it had already been applied by *H. Nozaki* et al. (ref. 8) for the chiral modification of organolithium and -magnesium compounds, though with limited success. *Guetté* et al. (ref. 9) reported in 1973 an asymmetric *Reformatzki* aldolization under the influence of (-)-sparteine. The Japanese group (ref. 8) also included the deprotonation and carboxylation of ethylbenzene to their studies, which produced (*R*)-(-)-2-phenylpropionic acid with low yield and *ee*. Most likely, this is not a result of an enantiotopic differentiation in the deprotonation step but of an equilibration of the diastereomeric benzylic ion pairs (ref. 10), being configurationally unstable and differing slightly in their energies.

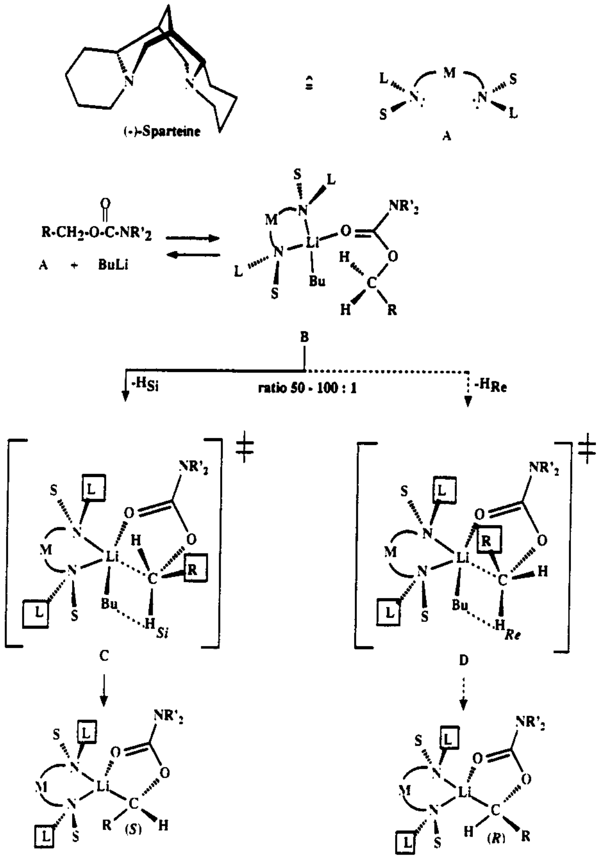
ENANTIOSELECTIVE DEPROTONATION OF ALKYL CARBAMATES

We'll demonstrate the principle of our method by the transformation of 1-heptanol into (*S*)-2-octanol (ref. 4) (*Scheme 5*). The deprotonation of the primary alkyl carbamate is carried out with a slight excess of *sec*-butyllithium/(-)-sparteine in ethereal solution at -78 °C. After quenching the carbanionic intermediates by methyl iodide, followed by deblocking the diastereomeric carbamate esters without separation, yielded (*S*)-2-octanol with 96 % *ee*. The deprotonation is facilitated by proximity effects and powerful dipol- and chelate stabilization (ref. 11) caused by the carbamate group (ref. 12). The double branching in the amino residue prevents nucleophilic attack of organolithium at the carbonyl group; on the other hand, being a part of an oxazolidine ring, as a consequence of the presence of an acid-labile aminoacetale moiety, makes easy deprotection possible.

Scheme 5



Scheme 6



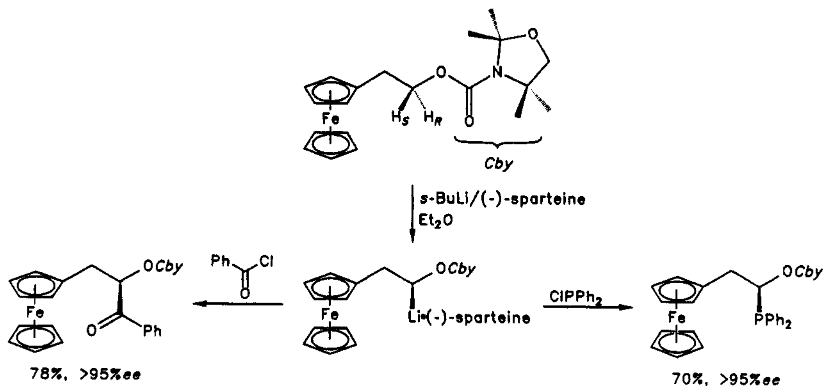
The stereoselection is a result of kinetic control in the deprotonation step (ref. 13), since the two diastereomeric ion pairs do not interconvert under the reaction conditions. Its ratio ($1S$: $1R \geq 50$) reflects a $\Delta G^{\#}$ of ≥ 1.5 kcal/mole in favour for the abstraction of the pro-*S* proton. The configurational stability of the carbanionic intermediates is essential in order to turn the efficient chiral recognition operating in the transition state to highly enantioenriched products. The size of the adjacent residue has only a minor influence, since the stereoselection already reaches the level of ≥ 95 % *ee* for the ethyl derivative ($R^1 = CH_3$) (ref. 13). Secondary alkyl carbamates, e. g. the isopropyl ester, are not deprotonated (ref. 14).

The energetic difference in the ground state stabilities of the diasteriomeric ion pairs is in the magnitude of few tenths of a kcal/mole (ref. 14). The energies of the competing diastereomorphic transition states, in which additionally the base is involved, could not be verified by calculation yet. As a working hypothesis we propose the following transition state model. Here we do not take into consideration that sparteine has no perfect C_2-symmetry and we simplify its structure to the bidentate ligand **A** (*Scheme 6*), carrying each a small (S) and a large (L) substituent at the stereogenic nitrogen atoms which are connected by a medium sized bridge M. The alkyl carbamate, *sec*-butyllithium (refs. 15,16) and (-)-sparteine form a complex **B** and the transprotonation proceeds intramolecularly via the competing diastereomorphic transition states **C** and **D**. Under assumption, that the branched *sec*-butyl residue seeks the steric interaction with one of the two smaller vicinities of the propeller-like sparteine molecule, its interaction with the H_S (ts **C**) causes much less steric repulsion than with H_R (ts **D**).

The deprotonation of unfunctionalized alkyl carbamates works uniformly well (refs. 4,5,17) and we'll focus on molecules which bear further functional groups or stereogenic centres.

The carbamate of 2-ferrocene-ethanol is enantioselectively deprotonated without any problem (ref. 18) (*Scheme 7*). Diphenylphosphinylation, and as well, benzoylation proceed with high enantiomeric excess. The latter example is noteworthy, since the acylation of organolithium compounds usually causes problems. The proton exchange with the more acidic ketone would give rise to partial racemization due to enolate formation. One might conclude from these (and many similar) experiments that the lithiocarbamate /(-)-sparteine complexes are very slow bases.

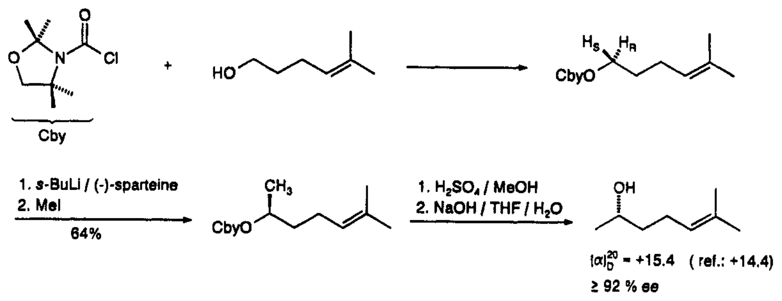
Scheme 7



Scheme 8 demonstrates the synthesis of (+)-(*S*)-sulcatol, a pheromone of *Gnathotrichus* species from 5-methyl-4-hexen-1-ol (ref. 17). The acid-catalyzed cleavage of the oxazolidine ring in the presence of the sensitive trisubstituted carbon double bond is somewhat tedious and has still to be optimized.

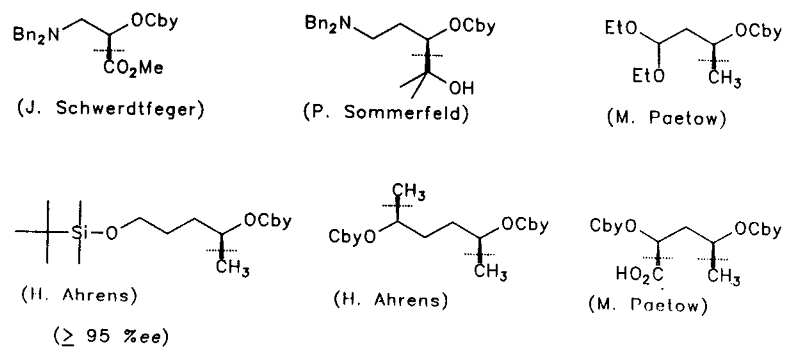
Further reactions, which all yield products with ≥ 95 % *ee*, are collected in *Scheme 9*. As these demonstrate, a *N,N*-dibenzylamino group in 2- or 3-position (refs. 19,20), acetale moieties (ref. 21), or 4-silyloxy- or carbamoyloxy groups (ref. 22) do not disturb. However, the internal complexation by 3-*N,N*-dimethylamino (ref. 20) or 3-carbamoyloxy groups (ref. 23) can be forced and causes interesting effects. Double substitution at both termini is possible; this was applied to the synthesis of stereochemically homogeneous 2-hydroxybutanolides (ref. 23).

Scheme 8

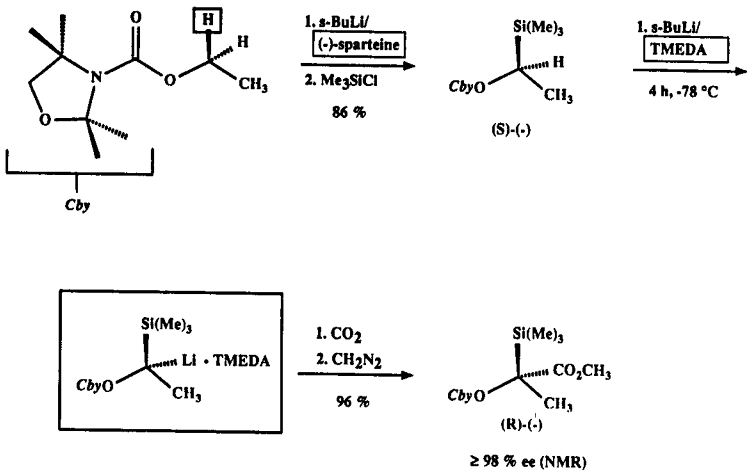


The deprotonation of α-hetero-substituted alkyl carbamates provides an access to new types of enantiomerically enriched chiral carbanions. The (*S*)-(-)-silane (≥ 98 % *ee*), produced from the ethyl carbamate, was deprotonated in the presence of the achiral complexant *N,N,N,N*-tetramethylethylenediamine (TMEDA) and the carbanionic intermediates after 4 h stirring at -78 °C in ether were quenched with carbon dioxide (refs. 13,17) (*Scheme 10*). Methylation of the crude acid afforded the (*R*)-(-)-ester with ≥ 98 % *ee* in essentially quantitative yield. It must be concluded from this result that the intermediate 1-carbamoyloxy-1-trimethylsilyl-ethyllithium has complete configurational stability under the reaction conditions.

Scheme 9



Scheme 10

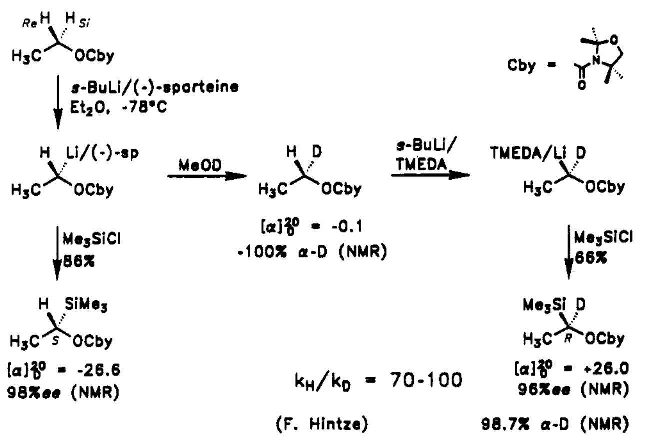


Configurational stability was also documented for the (-)-sparteine complexes of *t*-butoxy-carbonyl-2-lithio-pyrrolidines by *Beak* et al. (ref. 24). An unusually high kinetic H/D isotope effect in a deprotonation reaction was uncovered when we tried to deprotonate the (*S*)-1-deuterioethyl carbamate (ref. 13) (*Scheme 11*). The experiment was designed in order to examine whether the incoming electrophile and the removed proton occupy the same topological position. The anion formation with *sec*-butyllithium/(-)-sparteine proceeded very sluggishly, indicating that the chiral base refuses to attack the deuteron, though being attached to the preferred pro-*S* position. When the stereochemical restriction was lifted by using the achiral TMEDA instead of (-)-sparteine, a smooth deprotonation took place and on silylation the plus-rotatory silane, resulting from the substitution of the pro-*R* proton, was obtained with 96 % *ee*, bearing still 98.7 % of the original α-D. Consequently, the magnitude of the kinetic H/D isotope effect is at least 70. Most probably, it is the result of quantum-mechanical tunneling and a sterically highly restricted transition state. This efficient enantioselective synthesis, which relies on the efficient differentiation of an achiral reagent between isotopic substituents in enantiotopic positions, seems to be the first reported example of its kind. It might be useful for the preparation of stereochemically homogeneous, labelled alcohols.

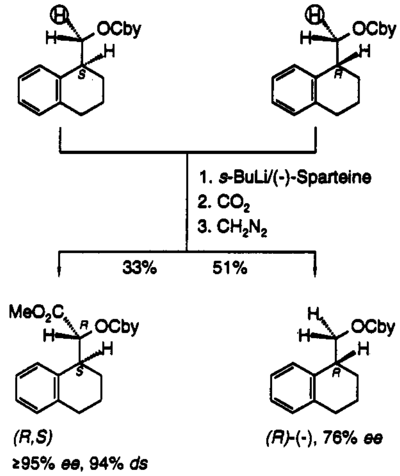
If a chiral, but racemic carbamate is offered, stereoselection is expected to occur on two levels: Besides the discrimination between pro-*S*- and pro-*R* protons of the same molecule, the chiral base will select the particular enantiomer in which the pro-*S* proton is best accessible. Indeed, an impressive kinetic resolution took place with the (1,2,3,4-tetrahydronaphth-1-yl)methyl carbamate (ref. 25), as shown in the self-explanatory *Scheme 12*.

A very high internal chiral induction was found in the carbamate of (*S*)-leucinol (ref. 19) (*Scheme 13*). The achiral base *sec*-butyllithium/TMEDA exclusively removes the pro-*R* proton, leading to stereochemically homogeneous products on methylation or carboxylation. Under the plausible assumption that the hetero-

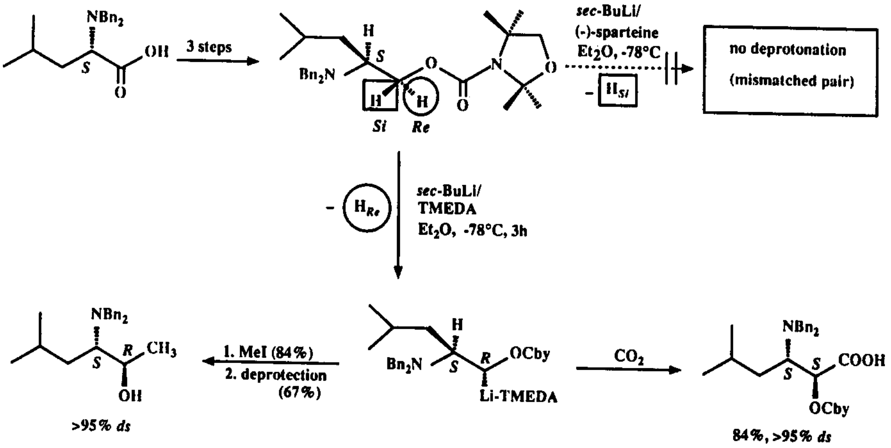
Scheme 11



Scheme 12

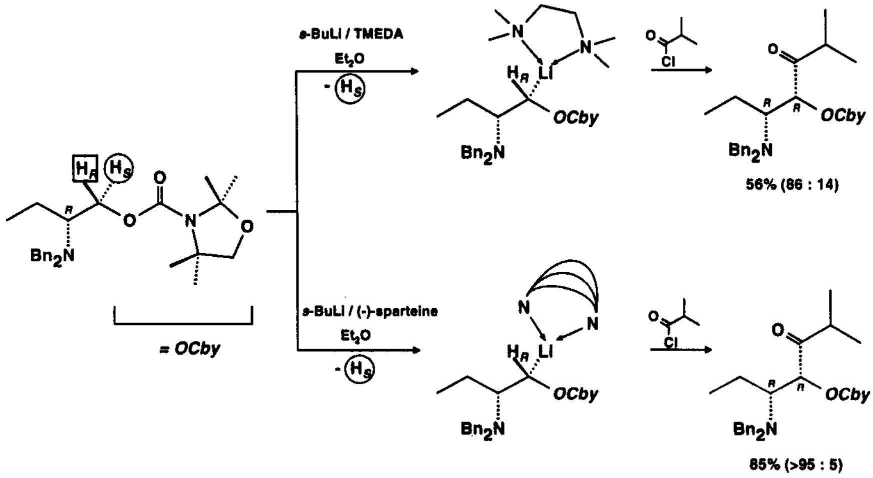


Scheme 13



substituents Bn_2N and O*Cby*, which both bear lone electron pairs, tend to occupy antiperiplanar positions, the better accessibility of the pro-*R* proton is evident. The combination (*S*)-carbamate and (-)-sparteine / *sec*-butyllithium constitutes the mismatched pair (ref. 26), because two strong chiral inductions oppose each other; here no reaction occurs even at the elevated temperature of -45 °C!

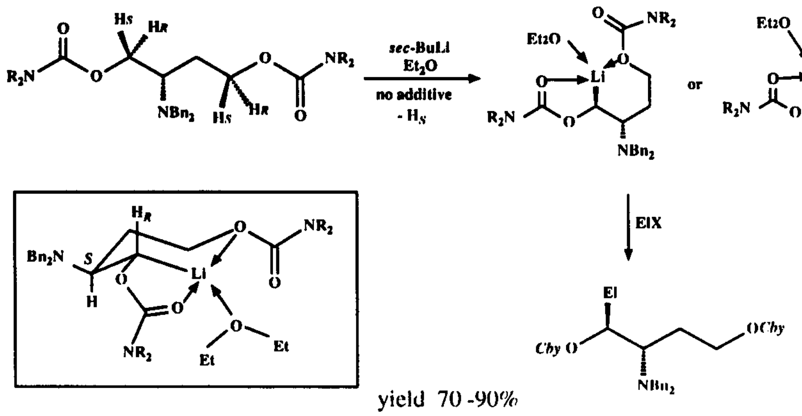
Scheme 14



On the other hand, in the carbamate of (*R*)-2-(*N,N*-dibenzylamino)-1-butanol, both the internal and external chiral induction have the same sence. As a consequence, the internal diastereoselectivity in favour for the pro-*S* proton of 7 : 1 is raised to > 20 : 1 in the presence of (-)-sparteine (ref. 27) (*Scheme 14*).

Complete diastereo- and regioselectivity in favour for the pro-*S*-1H is observed for the (*R*)-2-(*N,N*-dibenzylamino)-butane-1,4-diyl dicarbamate (ref. 28) (*Scheme 15*) when it is deprotonated in ethereal solution in the absence of a diamine. Presumably, the reaction course is governed by the complexation of the alkyllithium with both carbamate groups, giving rise to the formation of the sterically most favourable bicyclic chelate complex. Alternatively, a bicyclic chelate complex, having one eight-membered chelate ring, in which the remote (and more Lewis-basic) carbonyl oxygen atom is engaged, must be discussed.

Scheme 15

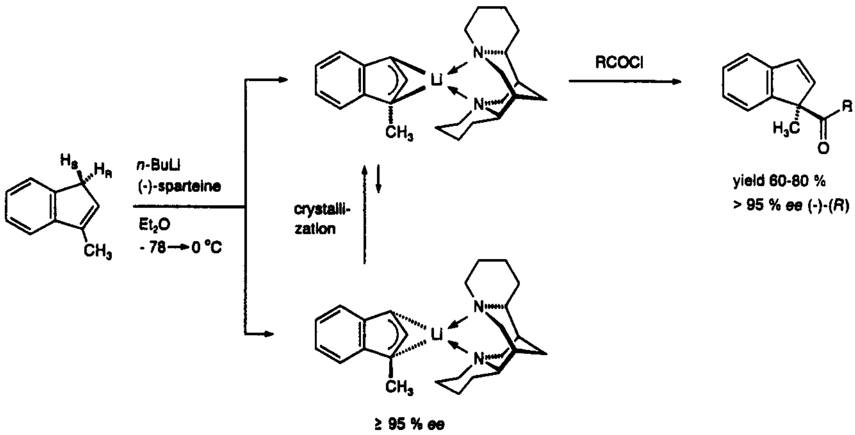


yield 70 -90%
regioselectivity > 95%
diastereoselectivity >95%

CHIRAL LITHIUM INDENIDES

In all examples of our work, presented above, a ***kinetically controlled*** selection and ***configurationally stable*** lithium carbanions were the origin of stereoselection. I like to disclose at the end the utilization of differences in the ***thermodynamic stabilities*** of ***configurationally labile*** lithium sparteine complexes in enantioselective synthesis. 1-Methylindene was deprotonated by means of *n*-butyllithium/(-)-sparteine and the ethereal solution of the diastereomeric ion pairs were allowed to equilibrate at 0 °C (ref. 29) (*Scheme 16*). The crystal suspension was quenched with several acid chlorides to afford essentially enantiopure alkyl 1-methylinden-1-yl ketones. Its (*R*)-configuration was established by its chemical correlation with (*R,R*)-1-methyl-*N*-(1-phenylethyl)-indene-1-carboxamide, which gave suitable crystals for an X-ray analysis (ref. 30). The configuration of the intermediate major lithium compound is still unknown and was proposed under the assumption of stereoretention in all carbonyl addition reactions.

Scheme 16



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REFERENCES

1. a) M. Murakata, M. Nakajmi, K. Koya, *J. Chem. Soc., Chem. Commun.* 1657 (1990); references. b) P. J. Cox, N. S. Simpkins, *Tetrahedron Asymmetry* 2, 1 (1991); references.
2. Reviews: a) D. Hoppe, T. Krämer, J.-R. Schwark, O. Zschage, *Pure and Appl. Chem. 62*, 1999 (1990). b) H. Kunz, H. Waldmann, *Chemtracts, Org. Chem. 3*, 421 (1990).
3. a) D. Hoppe, T. Krämer, *Angew. Chem. 98*, 171 (1986); *Angew. Chem., Int. Ed. Engl. 25*, 160 (1986). b) O. Zschage, J.-R. Schwark, T. Krämer, D. Hoppe, *Tetrahedron 48*, 8377 (1992).
4. D. Hoppe, F. Hintze, P. Tebben, *Angew. Chem. 102*, 1457 (1990); *Angew. Chem., Int. Ed. Engl. 29*, 1422 (1990). b) short review: P. Knochel, *Angew. Chem. 104*, 1486 (1993); *Angew. Chem., Int. Ed. Engl. 31*, 1459 (1993).
5. F. Hintze, D. Hoppe, *Synthesis* 1216 (1992).
6. For the first report on the configurational stability of 1-(alkoxymethoxy)alkyllithium see: W. C. Still, C. Sreekumar, *J. Am. Chem. Soc. 102*, 1201 (1980).
7. Review: K. Tomioka, *Synthesis* 541 (1990).
8. a) H. Nozaki, T. Aratani, R. Noyori, *Tetrahedron 27*, 905 (1971). b) H. Nozaki, T. Aratani, T. Toraya, *Tetrahedron Lett.* 4097 (1968).
9. M. Guetté, J. Capillon, J.-P. Guetté, *Tetrahedron 29*, 3659 (1973).
10. P. Beak, H. Du, *J. Am. Chem. Soc. 115*, 2516 (1993).
11. N. G. Rondan, K. N. Hook, P. Beak, W. J. Zajdel, J. Chandresekhar, P. v. Ragué Schleyer, *J. Org. Chem. 46*, 4108 (1981).
12. D. Hoppe, R. Hanko, A. Brönneke, F. Lichtenberg, *Angew. Chem. 93*, 1106 (1981); *Angew. Chem., Int. Ed. Engl. 20*, 1024 (1981).
13. D. Hoppe, M. Paetow, F. Hintze, *Angew. Chem. 105*, 430 (1993); *Angew. Chem., Int. Ed. Engl. 32*, 394 (1993).
14. E.-U. Würthwein, unpublished.
15. *sec*-Butyllithium is a chiral and racemic compound. Its replacement by isopropyllithium does not cause significant changes in stereoselectivity, see ref. R.
16. D. J. Gallagher, S. T. Kerrick, P. Beak, *J. Am. Chem. Soc. 114*, 5872 (1992).
17. F. Hintze, Dissertation, Univ. of Kiel, 1993.
18. I. Hoppe, unpublished.
19. J. Schwerdtfeger, D. Hoppe, *Angew. Chem. 104*, 1547 (1992); *Angew. Chem., Int. Ed. Engl. 31*, 1505 (1992).
20. P. Sommerfeld, D. Hoppe, *Synlett* 764 (1992).
21. M. Paetow, Dissertation, Univ. of Kiel, 1993.
22. M. Paetow, H. Ahrens, D. Hoppe, *Tetrahedron Lett. 33*, 5323 (1992).
23. H. Ahrens, M. Paetow, D. Hoppe, *Tetrahedron Lett. 33*, 5327 (1992).
24. S. T. Kerrick, P. Beak, *J. Am. Chem. Soc. 113*, 9708 (1991).
25. J. Haller, T. Hense, D. Hoppe, *Synlett* accepted.
26. Review: S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem. 97*, 1 (1985); *Angew. Chem., Int. Ed. Engl. 24*, 1 (1985).
27. S. Kolczewski, unpublished.
28. W. Guarnieri, Diploma Thesis, Univ. of Kiel, 1992.
29. I. Hoppe, D. Hoppe, manuscript in preparation.
30. G. Boche, M. Marsch, K. Harms, unpublished.