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Heteroatom-directed lithiations of chiral aklyl carbamates: A powerful tool for enantioselective synthesis

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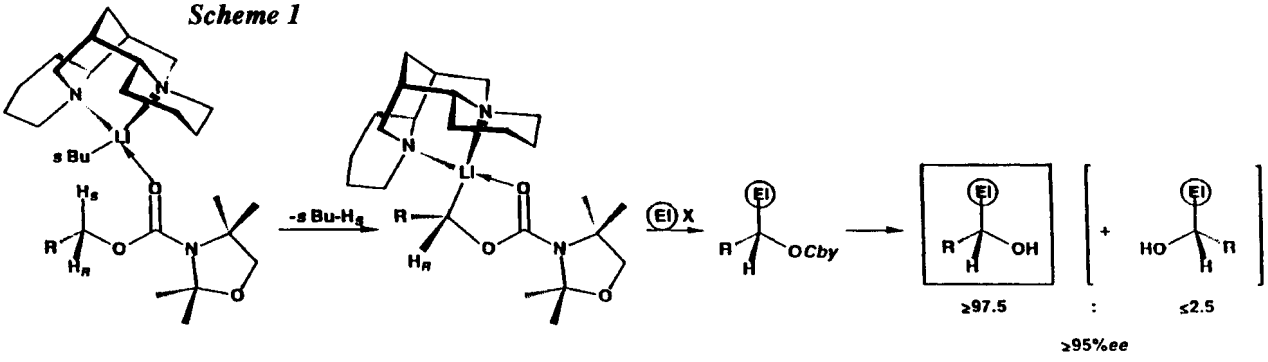
Abstract. Chiral alkyl carbamates, bearing hetero-substituents in the β- or γ-position, are deprotonated by *sec*-butyllithium/TMEDA with efficient selection between the diastereotopic α-methylene protons. Depending on the substitution pattern and the reaction conditions, either steric or chelate effects act as stereodirecting devices. In several cases, this substrate-induced stereoselectivity is enhanced or is overridden by means of *sec*-butyllithium/(-)-sparteine, which exhibits a strong preference for the abstraction of the pro-*S* proton. Altogether, an efficient and simple protocol for the stereoselective generation of synthetic equivalents for hetero-substituted α-oxy-alkanide synthons is presented.

Following the ideas of chelate stabilization and of proximity effects (ref. 1) to be powerful devices for directed deprotonation, we discovered in 1979 the strongly activating influence of *N,N*-dialkylcarbamoyloxy groups in the removal of adjacent protons of weak CH-acids by alkyllithium (ref. 2,3). 2-Alkenyl (ref. 2), benzyl (ref. 4) and 2-alkynyl (ref. 5) *N,N*-diisopropylcarbamates are deprotonated with great ease by *n*-butyllithium at low temperatures leading to stable five-membered chelate complexes (ref. 6), which smoothly react with several types of electrophiles. As it can be concluded from mechanistic studies on related systems (ref. 7), a complex is formed from the carbamate ester, butyllithium and the complexing diamine, eg. *N,N,N',N'*-tetramethylethylendiamine (TMEDA). The method was also successfully applied to aryl (ref. 8), 1-alkenyl (ref. 9) and 1,2-alkadienyl (ref. 10) carbamates by *Snieckus* et *al.*, by *Kocienski* et *al.*, and by our group. Even primary alkyl carbamates, derived from saturated alkanols, which lack of further carbanion-stabilizing groups, are deprotonated by *sec*-butyllithium/TMEDA (ref. 11). For the latter purpose we developed the 2,2,4,4-tetramethyl-1,3-oxazolidine-3-ylcarbonyl group (ref. 11). Here, a steric shielding, similar to that of the *N,N*-di-*tert.*-butylcarbamoyl group is warranted, but the acid-labile amino acetal moiety serves as the point of attack for the smooth deprotection to yield the racemic α-substituted alkanol. Overall, a very general protocol for the preparation of synthetic equivalents of α-hydroxy carbanions has been made possible.

As we reported in 1990 (ref. 11), replacing the diamine TMEDA by the naturally occurring alkaloid (-)-sparteine, which was introduced to organometallic chemistry in 1968 by *Nozaki* and *Noyori* (ref. 12), an efficient selection between the enantiotopic protons of the methylene group in the carbamate takes place (*Scheme 1*). Obviously, the proton transfer in the complex, preformed (ref. 7) from the alkyl carbamate, *sec*-butyllithium and (-)-sparteine, proceeds intramolecularly, resulting in a high difference in $\Delta G^{\neq}$ of the competing diastereomorphic transition states. Since the formed ion pairs are configurationally stable at the reaction conditions, trapping of these leads to substitution products with ≥ 95 % ee. The enantiomeric

Scheme 1

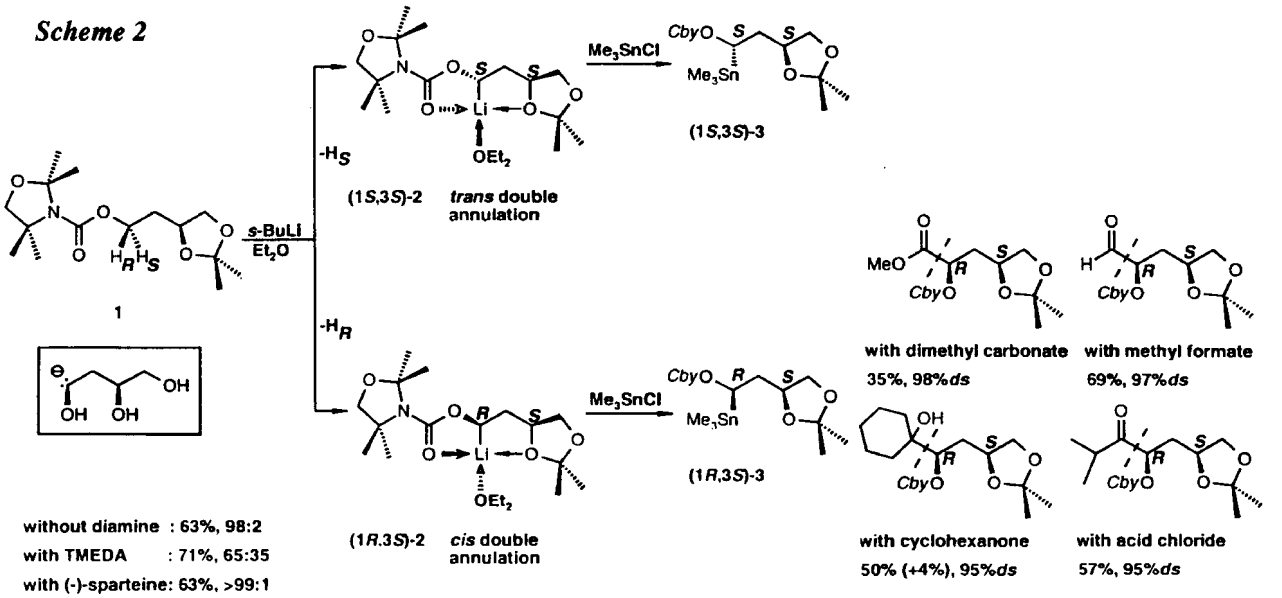


excesses achieved are essentially independent from the size of R and from the electrophile *El.* In all cases - except of these reported below - the pro-*S* proton is removed (ref. 13). Kinetically controlled deprotonations of other substrates, e.g. *N*-Boc-pyrrolidines (ref. 14) or 2-alkyl-*N,N*-diisopropylbenzamides (ref. 15), have been accomplished by *Beak* et *al.*

We have observed that the (-)-sparteine-induced deprotonation and silylation of the 3-(*N,N*-dimethylamino)propyl carbamate yields a racemic product, whereas the same reaction with the appropriate *N,N*-dibenzylamino derivative proceeds with 97 % *ee* (ref. 16). We explained the different reaction course by the intermediacy of a bicyclic chelate complex, in which the small Me_2N- (but not the bulky Bn_2N-) group acts as a good ligand to the lithium cation, keeping (-)-sparteine from intervention. In other cases, where a substituent of medium complexation ability is present in a favourable position, the stereochemical outcome depends on whether (-)-sparteine is added or not (ref. 17).

We investigated the 4-carbamate of (*S*)-1,2-di-*O*-isopropylidene-1,2,4-butanetriol, which is readily available from (*S*)-malic acid (ref. 18), under these aspects (*Scheme 2*) (ref. 19). It has, in a topological sense, the opposite configuration than the above mentioned (*S*)-butanediol derivative and, thus, *ul*-induction will support the removal of the pro-*S* proton. Indeed, the deprotonation and trimethylstannylation in ether as solvent, without additional complexing agent, yielded the expected diastereomer with 98 % ds. The presence of TMEDA causes a decrease to 65 % *ds*, whereas the addition of (-)-sparteine gave rise to a complete stereoselectivity (> 99 %) since external and internal chiral inductions are matched.

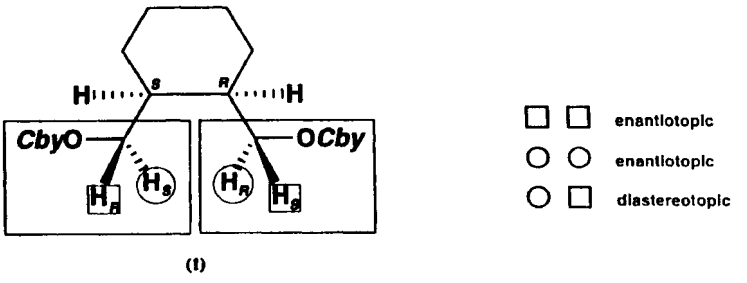
Scheme 2



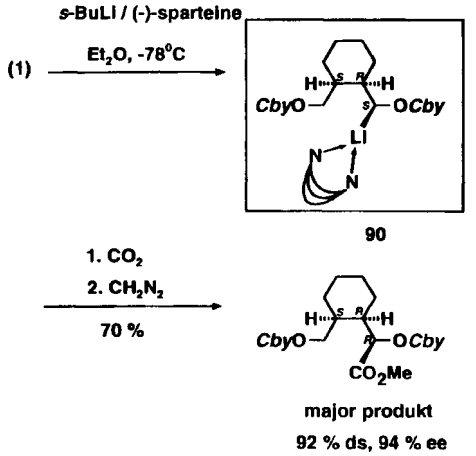
We noticed earlier that in the deprotonation of the (*S*)-1,4-pentanediyl dicarbamate, both chiral inductions (*lk* and pro-*S*) have the same direction (ref. 17). The *cis-meso*-1,2-(cyclohexane)dimethyl dicarbamate offers an interesting stereochemical situation (*Scheme 3*) (ref. 20). Both branches are enantiotopic, each bearing two diastereotopic α-methylene protons. Only one substituent can be placed in an equatorial position. The inspection of the molecule model led to the suggestion that the participation of the second carbamate group in the lithio derivative can not lead to a favourable tricyclic chelate complex. Evidence for this assumption comes from the following experiment: No deprotonation was achieved in the absence of a diamine with ether as a solvent (ref. 20). The TMEDA-assisted deprotonation, followed by carboxylation and ester formation gave the racemic (*S*,R*,R**)-diastereomer with 98 % *ds*, arising from the abstraction of one of the (enantiotopic) protons (*R*-pro-*S* or *S*-pro-*R*), revealing a powerful sterically directed 1,2-*ul* induction in the substrate.

In the presence of (-)-sparteine, the pro-*S* proton being best accessible (*R*-pro-*S*) is preferentially selected and the (*S,R,R*)-diastereomer is formed with 94 % *ee* and 92 % *ds* (*Scheme 4*). Two out of the three possible further diastereomeric lithium-(-)-sparteine complexes are formed to a minor extent. This reaction can be regarded to constitute an intramolecular case of the kinetic resolutions of racemic alkyl carbamates via sparteine-assisted deprotonation (ref. 21). Some transformations of the adduct are shown in Scheme 5 (ref 20).

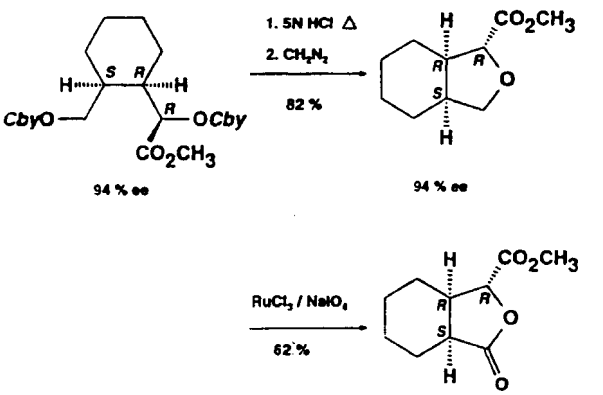
Scheme 3



Scheme 4

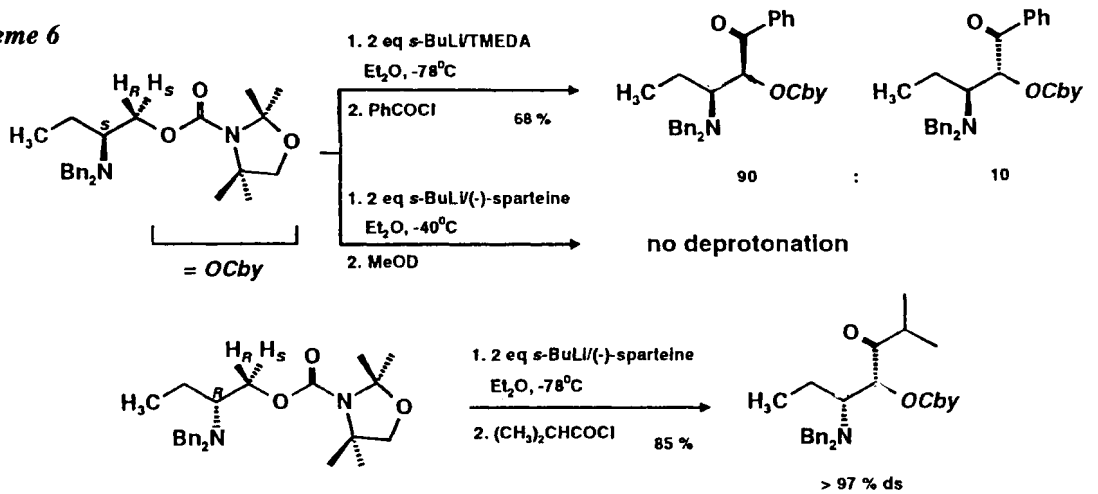


Scheme 5

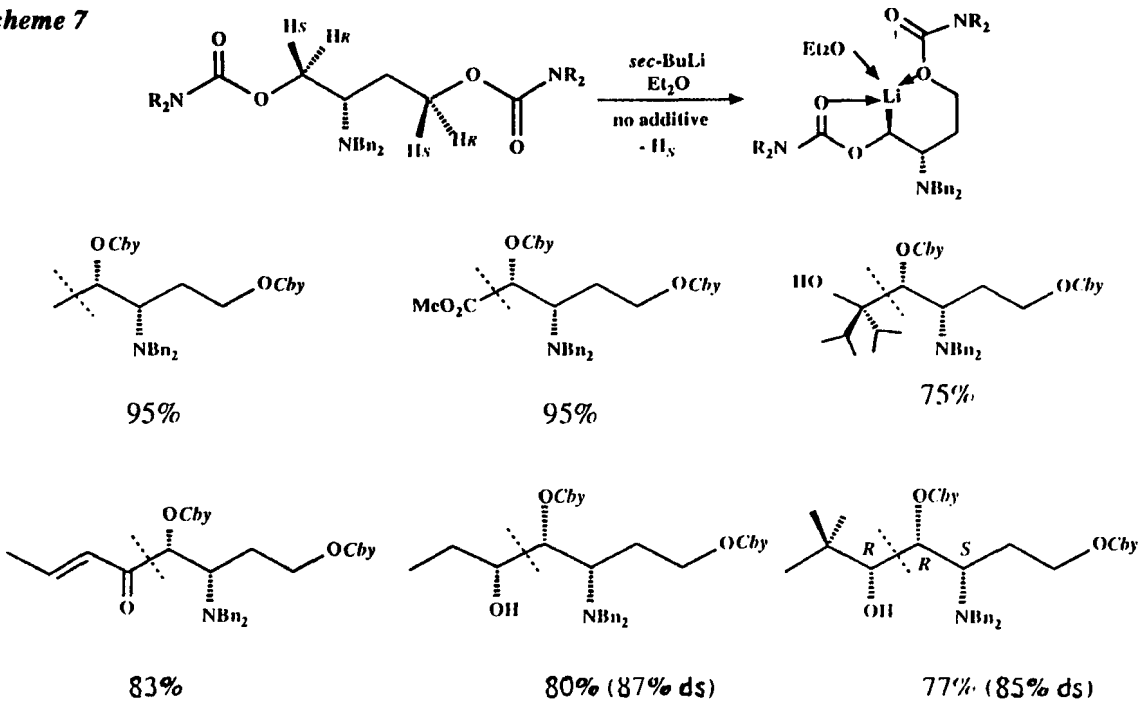


Achiral and chiral 2-(*N,N*-dibenzylamino)alkyl carbamates are also deprotonated without interference of a chelating ligand and the stereoselection is also mainly directed by steric effects (ref. 22). As a result of a strong *ul*-induction in the carbamate of (*S*)-2-(*N,N*-dibenzylamino)butanol, *sec*-butyllithium/TMEDA removes the pro-*R* proton, yielding after benzoylation the (*S,R*)-ketone (*Scheme 6*) (ref. 23), however the (-)-sparteine complex, which is "specialized" to pro-*S* protons does not react at all. When using the (*R*)-carbamate, the matched pair is given and the abstraction of the pro-*S* proton proceeds smoothly with extremely high diastereoselectivity.

Scheme 6



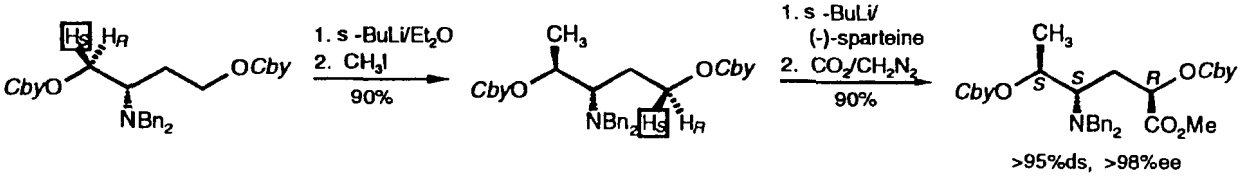
Scheme 7



The situation is more complicated in the dicarbamate of (*S*)-2-(*N,N*-dibenzylamino)-1,4-butanediol, easily obtained from (*S*)-aspartic acid (*Scheme 7*) (ref 24). Four protons in regioisomeric and diastereotopic positions, respectively, compete. When no diamine is present, the 2-H_S is removed exclusively, yielding with a wide range of electrophiles stereohomogeneous substitution products with high yields and essentially complete stereoselectivity (ref. 24). This result indicates, that the features of a favourable bicyclic chelate complex, which involves the 4-carbamoyloxy group and places the bulky dibenzylamino group in an equatorial position, already dominate the transition state. The importance of a chelating group in 4-position is seen from the following experiments: The 4-*O*-TBDMS-derivative does not react, but the 4-methyl ether, again, is deprotonated smoothly (ref. 24).

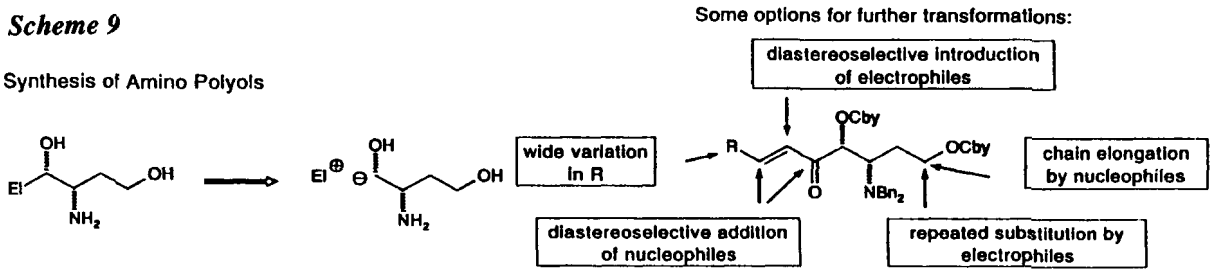
In a second, (-)-sparteine-assisted step 4-H_S can be substituted too, as it is shown in the synthesis of a protected (2*R*,4*S*,5*S*)-4-amino-2,5-dihydroxyhexanoic acid (*Scheme 8*) (ref. 24).

Scheme 8

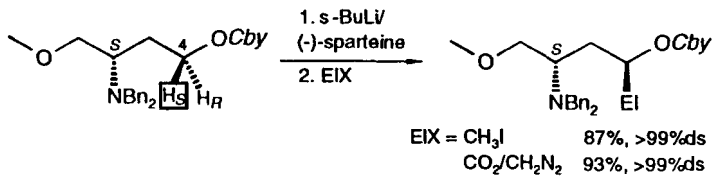


Scheme 9 gives an impression of the manifold of possibilities offered by the methods (outlined for the product obtained from crotonoylation (ref 24).

Scheme 9

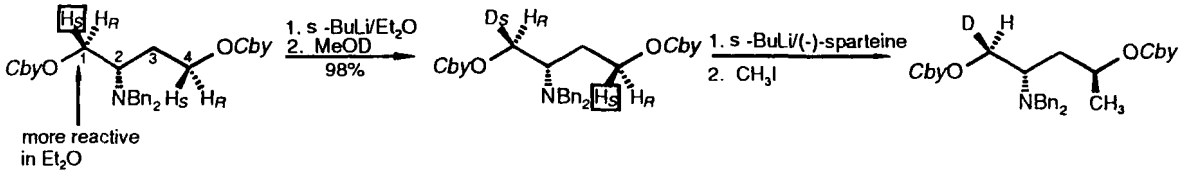


Scheme 10



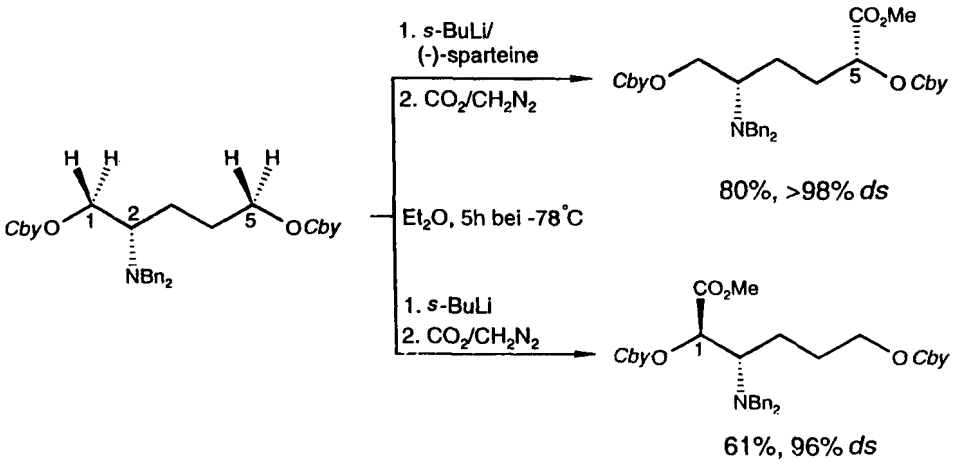
By which means a monosubstitution in 4-position can be achieved? The more conventional route makes use of the 1-*O*-methyl 4-carbamate ester (*Scheme 10*) (ref. 24). A more elegant solution is given by blocking the 1-position through deuteriation, since we had previously discovered extremly high kinetic H/D isotope effects of > 60 in the deprotonation of alkyl carbamates (ref S). The dicarbamate was deprotonated under chelate control, the anion trapped with CH_3OD, and the deuterio derivative now is further converted by the (-)-sparteine method, giving rise to a clean substitution of the 4-H_S (*Scheme 11*).

Scheme 11



A similar, but more pleasant situation, arises with the dicarbamate of (*S*)-2-(*N,N*-dibenzylamino)-1,5-pentanediol, derived from (*S*)-glutamic acid (*Scheme 12*) (ref 24). The chelate-controlled removal and substitution of 1-H_S is possible, although it proceeds sluggishly presumable due to unfavourable ring size. If (-)-sparteine is present, the preference for the 1-H is overridden, leading to a highly selective substitution of 5-H_S.

Scheme 12



Altogether, the methods outlined above, render a facile and flexible access to a manifold of poly-substituted, stereochemically homogeneous amino hydroxy compounds.

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References

1. a) P. Beak, A. I. Meyers, *Acc. Chem. Res. 19*, 356 (1986) and references. b) N. G. Rondan, K. N. Houk, P. Beak, W. J. Zajdel, J. Chandrasekhar, P. v. R. Schleyer, *J. Org. Chem. 46*, 4108 (1981).
2. a) D. Hoppe, R. Hanko, A. Brönneke, *Angew. Chem. 92*, 637 (1980); *Angew. Chem., Int. Ed. Engl. 19*, 625 (1980). b) D. Hoppe, R. Hanko, A. Brönneke, F. Lichtenberg, *Angew. Chem. 93*, 1106 (1981); *Angew. Chem., Int. Ed. Engl. 20*, 1024 (1981). c) R. Hanko, D. Hoppe, *Angew. Chem. 93*, 115 (1981); *Angew. Chem., Int. Ed. Engl. 20*, 127 (1981).
3. Review: D. Hoppe, T. Krämer, J.-R. Schwark, O. Zschage, *Pure and Appl. Chem. 62*, 1999 (1990).
4. a) D. Hoppe, A. Brönneke, *Synthesis* 1045 (1982). b) A. Carstens, D. Hoppe, *Tetrahedron 50*, 6097 (1994). c) P. Zhang, R.E. Gawley, *J. Org. Chem. 58*, 3223 (1993).
5. D. Hoppe, C. Riemenschneider, *Angew. Chem. 95*, 64 (1983); *Angew. Chem., Int. Ed. Engl. 22*, 54 (1983).
6. For an X-ray analysis see: M. Marsch, K. Harms, O. Zschage, D. Hoppe, G. Boche, *Angew. Chem. 103*, 338 (1991); *Angew. Chem., Int. Ed. Engl. 30*, 321 (1991).
7. D. J. Gallagher, S. T. Kerrick, P. Beak, *J. Am. Chem. Soc. 114*, 5872 (1992).
8. M. P. Sibi, V. Snieckus, *J. Org. Chem. 48*, 1935 (1983).
9. a) P. Kocienski, N. J. Dixon, *Synlett* 52 (1989). b) S. Sengupta, V. Snieckus, *J. Org. Chem. 55*, 5680 (1990). c) P. Kocienski, S. Wadman, K. Cooper, *J. Am. Chem. Soc. 111*, 2363 (1989). d) V. Snieckus, *Pure and Appl. Chem. 62*, 2047 (1990). e) P. Kocienski, C. Barber, *Pure and Appl. Chem. 62*, 1933 (1990).
10. D. Hoppe, C. Gonschorrek, *Tetrahedron Lett. 28*, 785 (1987).
11. a) D. Hoppe, F. Hintze, P. Tebben, *Angew. Chem. 102*, 1457 (1990); *Angew. Chem., Int. Ed. Engl. 29*, 1422 (1990). b) F. Hintze, D. Hoppe, *Synthesis* 1216 (1992). c) D. Hoppe, F. Hintze, P. Tebben, M. Paetow, H. Ahrens, J. Schwerdtfeger, P. Sommerfeld, J. Haller, W. Guarnieri, S. Kolczewski, T. Hense, I. Hoppe, *Pure and Appl. Chem. 66*, 1479 (1994).
12. a) H. Nozaki, T. Aratani, R. Noyori, *Tetrahedron 27*, 905 (1971). b) H. Nozaki, T. Aratani, T. Toraya, *Tetrahedron Lett.* 4097 (1968).
13. D. Hoppe, M. Paetow, F. Hintze, *Angew. Chem. 105*, 430 (1993); *Angew. Chem., Int. Ed. Engl. 32*, 394 (1993).
14. S. T. Kerrick, P. Beak, *J. Am. Chem. Soc. 113*, 9708 (1991).
15. S. Thayumanavan, S. Lee, C. Liu, P. Beak, *J. Am. Chem. Soc. 116*, 9755 (1994).
16. P. Sommerfeld, D. Hoppe, *Synlett* 764 (1992).
17. a) M. Paetow, H. Ahrens D. Hoppe, *Tetrahedron Lett, 33*, 5323 (1992). b) H. Ahrens, M. Paetow, D. Hoppe, *Tetrahedron Lett, 33*, 5327 (1992).
18. S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, T. Moriwake, *Chemistry Lett.* 1389 (1984).
19. H. Helmke, unpublished.
20. H. Ahrens, Dissertation, Univ. of Münster, 1994.
21. J. Haller, T. Hense, D. Hoppe, *Synlett* 726 (1993).
22. J. Schwerdtfeger, D. Hoppe, *Angew. Chem. 104*, 1547 (1992); *Angew. Chem., Int. Ed. Engl. 31*, 1505 (1992).
23. S. Kolczewski, unpublished.
24. W. Guarnieri, M. Grehl, D. Hoppe, *Angew. Chem. 106*, 1815 (1994), *Angew. Chem., Int. Ed. Engl. 33*, 1734 (1994).