

Metal, ligand and protective group tuning as a means to control selectivity

M. T. Reetz

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1,
4330 Mülheim an der Ruhr, Germany

Abstract - Chemo- and stereoselective Grignard addition reactions are possible if ligand tuning is applied, as in the magnesiation of alkylolithium reagents with magnesium tosylates or carboxylates. Protective groups tuning is another important instrument. Thus, N,N-dibenzyl-amino aldehydes react with a variety of organometallics under non-chelation control. The nature of the protective group is also important in reactions of α -amino aldimines and electron-poor γ -aminoolefins (including peptide derivatives).

INTRODUCTION

Selectivity continues to be a major point of interest in organic synthesis. More than a decade ago we introduced the concept of titanation as a means to control "carbanion selectivity" (ref. 1). Accordingly, classical "carbanions" are transmetalated by titanating agents of the type ClTiL_3 , thereby generating organotitanium reagents which undergo chemo-, regio- and stereoselective C-C-bond forming reactions (Grignard-type, aldol, Michael additions, substitution reactions, etc). By choosing the proper ligands L at titanium, the electronic and steric properties of the reagents can be adjusted (Fig. 1) (ref. 2).

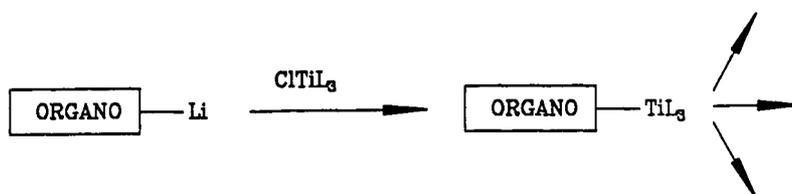


Fig. 1. Titanation as a means to control carbanion-selectivity (L = Cl, OR, NR₂, etc.)

For example, if L = Cl, the organotitanium trichlorides are quite Lewis acidic, making them ideal reagents for chelation controlled additions to chiral α - and β -alkoxy aldehydes (ref. 3). The sense of such diastereofacial selectivity can be reversed by using electron-donating ligands such as alkoxy or amino groups, although the degree of non-chelation control is not always high (ref. 3). This has to do with the fact that too many different conformations of the aldehydes can react, in contrast to the rigid intermediate Cram-type chelates in chelation controlled reactions. The same problems arise in optimizing Cram-selectivity in addition reactions of α -chiral aldehydes devoid of hetero-atoms. Nevertheless, notable improvements have been made using bulky alkoxy or amino ligands (ref. 1,4), including chiral versions (ref. 5).

This as well as other work has led to the expressions "metal tuning" and "ligand tuning". Thus, a number of other metals have been employed in transmetalation for the purpose of controlling chemo- and stereo-selectivity (ref. 6), including Imamoto's cerium reagents (ref. 7). However, the ligands have not been varied widely. Rather, particular metal salts were chosen because they happen to be commercially available or most easily accessible. This is somewhat surprising, especially in view of the fact that ligand tuning in titanium chemistry is known to be an important factor in maximizing selectivity. We have therefore recently embarked on an extensive research effort in which ligands are systematically varied for certain transmetalating agents, especially those involving magnesium, manganese, cerium and iron. Below we report on our initial experience concerning ligand tuning in Grignard addition reactions.

Another important instrument in chemo- and stereoselective carbonyl addition reactions concerns the choice of the protective group. This has been termed protective group tuning (ref. 8). It turns out that a protective group in a polyfunctional molecule not only protects a certain functional group, it can also dictate the sense and magnitude of diastereofacial selectivity (ref. 8,9). We have recently developed this concept systematically in Grignard-type and aldol additions to α -amino aldehydes and α -amino imines and in Michael-type reactions of electron-poor γ -aminoolefins. The results are reviewed in the second part of this article.

LIGAND EFFECTS IN GRIGNARD ADDITION REACTIONS

In Grignard addition reactions of RMgX ($X = \text{Cl, Br, I}$) the nature of the halide generally plays no significant role in stereochemically relevant situations (ref. 10). In rare cases other ligands such as alkoxy or amino moieties have been tested, but the benefits have not become apparent (ref. 11). Due to the basic nature of such ligands, side reactions initiated by undesired deprotonation may be the cause of low yields of Grignard adducts.

Our initial interest in potential ligand effects in Grignard reactions focused on the use of tosyl and carboxyl moieties, which are not expected to be basic. Although several synthetic routes to such "second generation" Grignard reagents can be envisaged, the scheme shown in Fig. 2 was utilized first (ref. 12). Accordingly, an organolithium reagent is transmetalated by the proper magnesium salt MgL_2 :

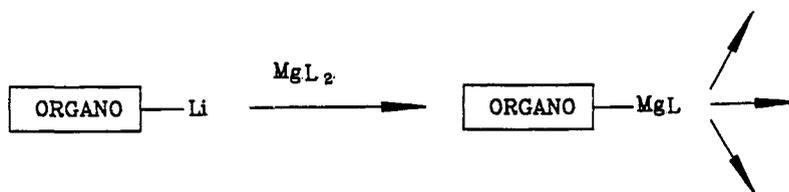
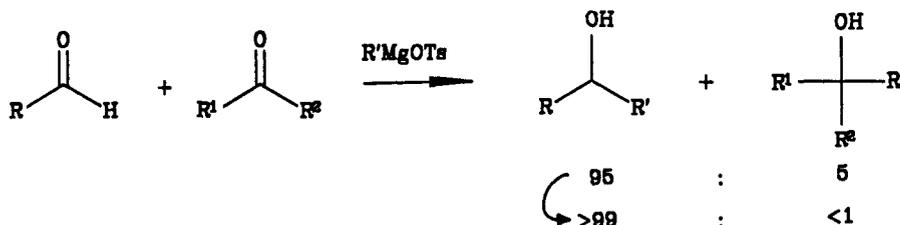


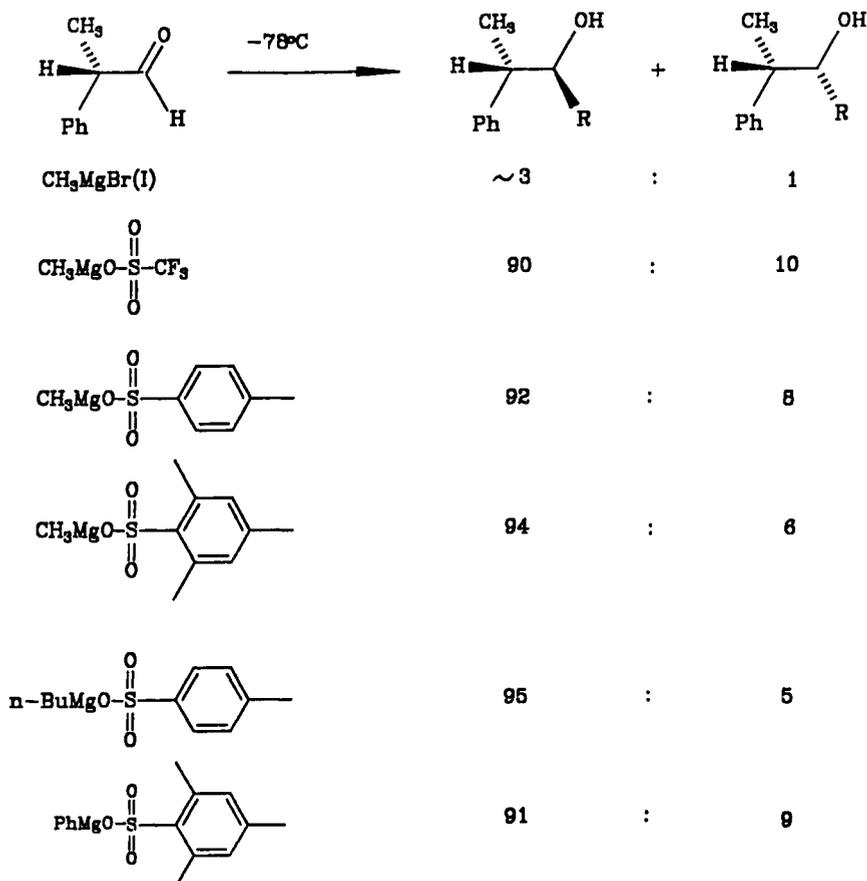
Fig. 2. Magnesium as a means to control carbanion-selectivity

Tosyl and related ligands

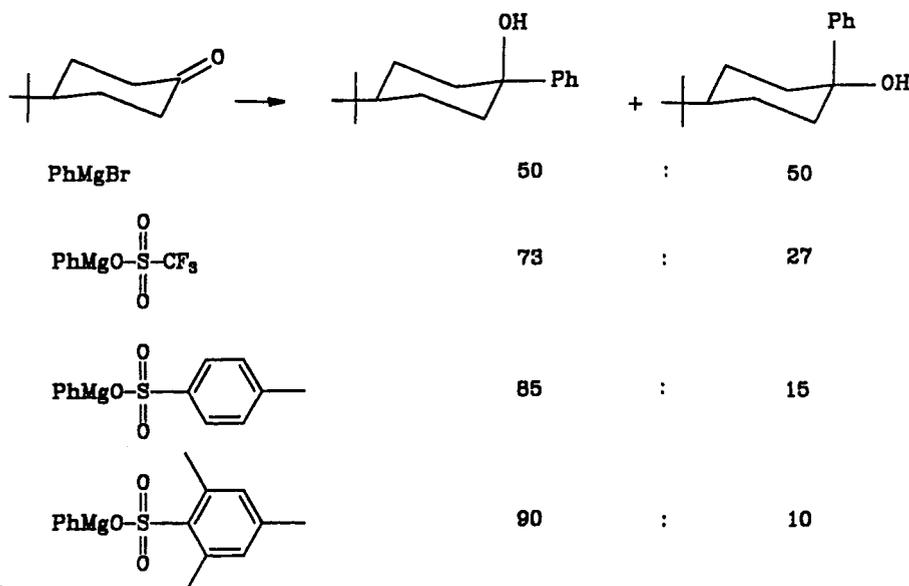
Upon reacting alkyl- and aryllithium compounds $\text{R}'\text{Li}$ with $\text{Mg}(\text{OSO}_2\text{R})_2$ in ether, magnesium reagents $\text{R}'\text{MgOSO}_2\text{R}$ are formed which readily add to aldehydes and ketones, the yields being comparable to those involving classical Grignard reagents (70 - 95%). The real benefits of this methodology became apparent when testing the new reagents in chemo- and stereochemically relevant cases (ref. 12). For example, complete or nearly complete aldehyde-selectivity was observed in competition experiments. This behavior is quite similar to the chemoselectivity observed for organotitanium reagents. However, many of the limitations of titanium chemistry such as β -hydride elimination do not pertain to magnesium reagents! The precursors $\text{R}'\text{Li}$ behave chemorandomly (ref. 1,2,5). The corresponding classical Grignard reagents $\text{R}'\text{MgCl}$ deliver 2 : 1 to 3 : 1 mixtures of aldehyde and ketone adducts. It is tempting to ascribe the beneficial effects of tosyl ligands to steric factors, as in the case of organotitanium reagents (ref. 2,4). However, other factors may be involved and several questions remain unanswered: What is the role of the Schlenk equilibrium? Is the lithium salt (e. g., LiOSO_2R) involved in the reagent via complexation or in the carbonyl component via coordination? Are the reagents monomers or aggregates? Thus detailed discussions of the mechanism are not warranted presently.



We have also observed positive ligand effects in stereochemically relevant cases. For example, controlling Cram-selectivity in reactions of 2-phenylpropanal poses no problems (ref. 12). The results are at least as good or even better than in the case of bulky titanium reagents, e. g., $\text{CH}_3\text{Ti}(\text{OPh})_3$ (ref. 4). Again, the limitations of Ti-chemistry do not pertain to magnesium reagents.



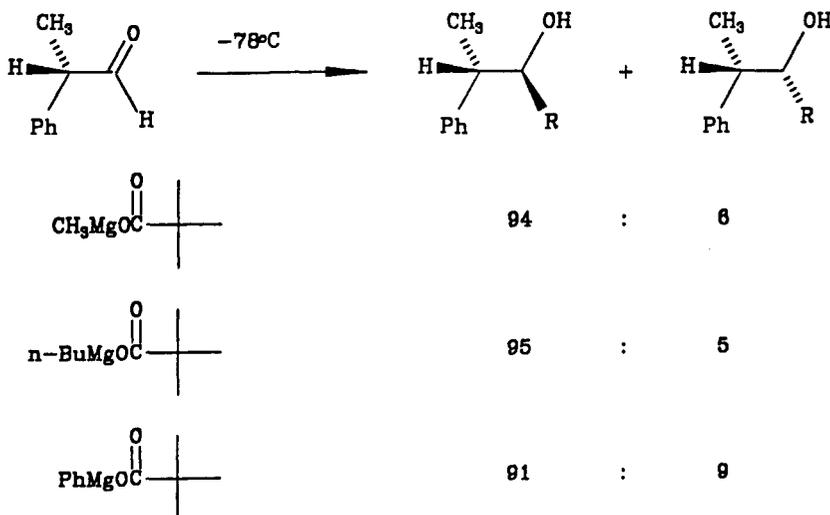
Another stereochemically difficult situation relates to the addition of arylmetal reagents to cyclohexanone derivatives (axial/equatorial-selectivity). This is due to the fact that in the reactions of such "flat" reagents 1,3-diequatorial interactions (axial attack) are similar in energy to torsional strain (equatorial attack). Here the ligand effects of the Grignard additions are indeed dramatic, since diastereoselectivity increases from 50 : 50 to 90 : 10! In the case of 3-methylcyclohexanone, selectivity is 95% (ref. 12).



Carboxyl ligands

Initially it was not clear whether organolithium reagents can be magnesiated using magnesium salts of carboxylic acids, since nucleophilic addition to the carbonyl functionality could occur (similar to the Gilman ketone synthesis). Indeed, treating methyllithium with the magnesium salt of trifluoroacetic acid followed by the addition of benzaldehyde did not result in any appreciable amount of the expected Grignard adduct. Fortunately, this problem arises only in the case of carboxyl groups bearing strongly

electron-withdrawing moieties, because this renders the carboxylate C-atom electrophilic and therefore prone to undesired nucleophilic attack. The magnesium salts of all other carboxylic acids tested so far are excellent magnesiating agents, including $\text{Mg}(\text{OAc})_2$. They all convert organolithium reagents into organomagnesium carboxylates which in turn add smoothly to aldehydes and ketones (70 - 95% yields), chemo- and stereoselectivity being comparable or better than in the case of the tosyl analogs. A case in point is the observed Cram-selectivity of alkyl- and arylmagnesium pivalates (ref. 12).



Here again the reagents pictured above may well be an oversimplification of the actual structure. Interestingly, the pivalates are all soluble in the reaction medium (ether), a property which does not always pertain in the case of the tosylates. Therefore, future structural studies of carboxylates are likely to be easier.

Nitrogen-based ligands

A wide variety of nitrogen-based ligands can be envisaged, especially those which contain electron-withdrawing groups such as sulfonyl moieties. The latter requires the conversion of sulfone amides into the corresponding magnesium salts which can then be utilized as magnesiating agents. Initial results are promising. Moreover, we have discovered that electron-withdrawing groups at nitrogen are not necessarily required (ref. 13).

Evaluation of the initial results

The use of the "second generation" Grignard reagents of the type described here constitutes a promising approach to controlling chemo- and stereoselective C-C-bond forming reactions. Work is in progress concerning structural and mechanistic aspects. The feasibility of enantioselective reactions based on chiral carboxylates as ligands is also being studied. Moreover, it remains to be seen whether "carbanions" in general, i. e., lithiated C-H acidic compounds such as sulfones, nitriles, esters, ketones, heterocycles, etc. can be magnesiated and reacted selectively. In many of these cases the problem of simple diastereoselectivity arises. Although magnesium enolates of ketones and esters are seldomly used in stereoselective aldol additions, the presence of bulky and/or chiral ligands could open up new avenues for organic synthesis. Finally, preliminary reactions of the new magnesium reagents in the presence of Cu(I) salts show that conjugate additions to α,β -unsaturated ketones are possible. The initial experience gained in the area of organomagnesium chemistry shows that it is worthwhile to explore new ligand systems. We have therefore started to look for similar effects in the case of other metals, especially manganese(II), iron(II) and cerium(III).

PROTECTIVE GROUP TUNING

Background

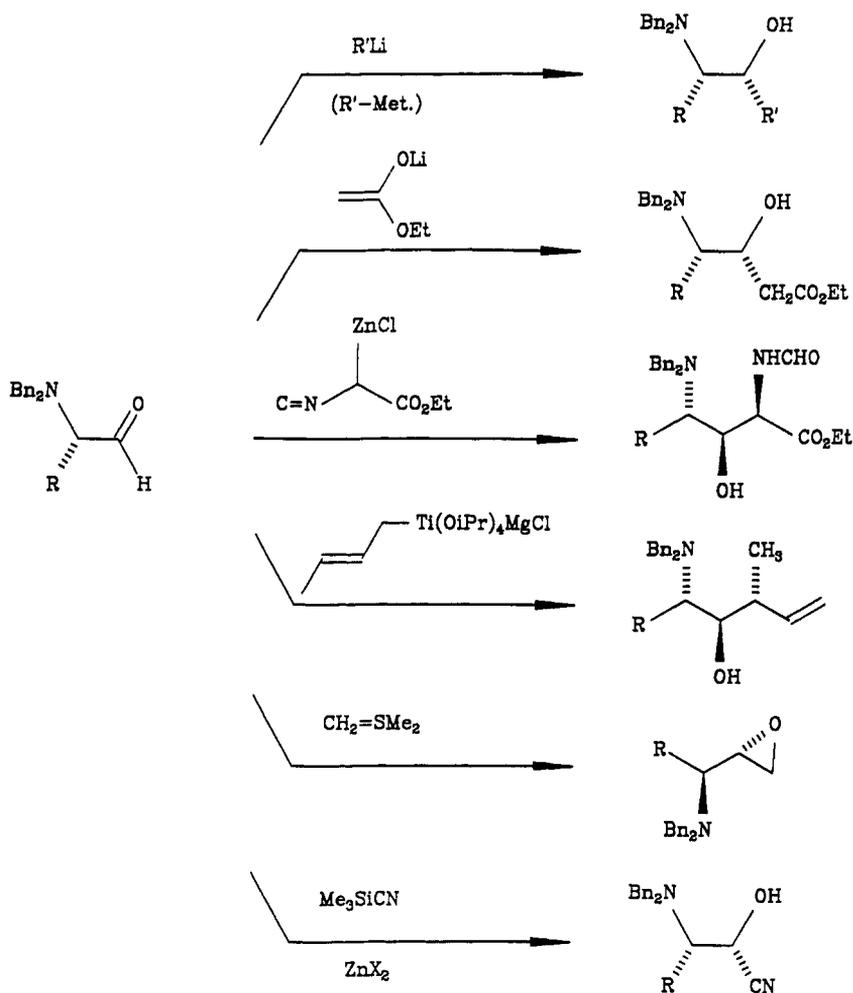
Although protective groups are generally employed for the sole purpose of preventing undesired side reactions, they can also be used to direct the sense and magnitude of diastereofacial selectivity. Scattered reports of reduction (ref. 9,14), Grignard-type (ref. 15,16) and aldol additions (ref. 16) involving chiral alkyl- and silyl-protected hydroxy ketones have appeared in the literature. Nevertheless, the concept of protective group tuning needs to be developed more systematically. Indeed, our recent work concerning protected α -amino aldehydes, α -amino aldimines and electron-poor γ -aminoolefins derived from amino acids shows that the variation of the protective group at nitrogen has a dramatic influence on stereoselectivity (ref. 17).

α -Amino aldehydes as chiral building blocks

Many attempts have been made to convert α -amino acids into α -amino aldehydes and to use the latter in stereoselective Grignard-type and aldol additions as well as cyanohydrin-forming reactions (ref. 18). Generally, protective groups such as BOC-moieties (t-butoxycarbonyl) have been used. With a few notable exceptions (ref. 17,18), no general methods for diastereofacially selective additions have become available. For example, most BOC-protected α -amino aldehydes react with RMgX , RLi , lithium enolates and HCN/KCN to produce 1 : 1 or 2 : 1 mixtures of diastereomers. Another problem concerns the ease of racemization of such aldehydes: They must be handled in cold ether (ref. 18), and even then some racemization (3 - 5%) may occur (ref. 19).

We originally entered this field hoping to apply metal and ligand tuning to the above aldehydes. However, we were not able to work out general procedures for chelation or non-chelation controlled addition reactions. This is in contrast to our work on chelation controlled additions to chiral α - and β -alkoxy aldehydes, in which Lewis acidic reagents (e. g., CH_3TiCl_3) or Lewis acids such as TiCl_4 , SnCl_4 or MgBr_2 in combination with C-nucleophiles such as R_2Zn , Me_3SiCN , enol- and allylsilanes are used (ref. 3). Therefore, a different strategy had to be developed, namely protective group tuning. The idea was to use two protective groups, e. g., benzyl groups (ref. 20). The corresponding N,N -dibenzylamino aldehydes are easily prepared from amino acids and can be handled at room temperature without any signs of racemization.

The crucial question regarding the utility of such aldehydes concerned the sense and magnitude of stereoselectivity of addition reactions. Upon reacting the aldehydes with Grignard and alkyllithium reagents, we experienced two surprises: Firstly, high degrees of diastereoselectivity were observed ($\text{ds} > 90\%$). Secondly, the sense of diastereoselectivity turned out to be non-chelation controlled. Thus, although an amino group might be expected to participate in the formation of intermediate Cram-type chelates, such phenomena are not operating. Although the molecules are not "tied up", stereoselectivity is high. In other situations non-chelation control is generally difficult and not uniformly high, i. e., in reactions of organotitanium reagents of low Lewis acidity [e. g., $\text{RTi}(\text{OiPr})_3$] with chiral α -alkoxy aldehydes (ref. 2,3,16).



Thus, α -N,N-dibenzylamino aldehydes behave completely differently than analogous α -benzyloxy aldehydes. The high propensity of α -N,N-dibenzyl-amino aldehydes to react in a non-chelation controlled manner is also apparent in reactions of organocerium reagents RCeCl_2 and cuprates R_2CuLi (ref. 17,20). In rare cases the classical Li or Mg reagents are so reactive that diastereoselectivity is mediocre, e. g., allylmagnesium chloride delivers 1 : 3 diastereomer ratios in favor of non-chelation. In such cases titanation using $\text{ClTi}(\text{OiPr})_3$, $\text{Ti}(\text{OiPr})_4$ or $\text{ClTi}(\text{NEt}_2)_3$ produces tamed allyltitanium reagents (ref. 4) which add selectively to the N,N-dibenzylamino aldehydes. Other C-nucleophiles such as Li-enolates (ref. 20,21), enolsilanes/ MgX_2 (ref. 22), $\text{Me}_3\text{SiCN}/\text{ZnX}_2$ (ref. 23) and sulfur ylids (ref. 8) also add in a non-chelation controlled manner. In the case of prochiral enolates or crotyltitanium reagents, control of simple diastereoselectivity is also possible, i. e., essentially one of four possible diastereomers are formed. A number of other research groups have utilized the N,N-dibenzylamino aldehydes in related reactions (ref. 24).

Although the results are in line with the Felkin-Anh model (ref. 25), they can also be accommodated by ground state arguments. The X-ray structural analysis of the aldehyde derived from phenylalanine (Fig. 3) shows that the back side of the carbonyl π -bond is sterically shielded (ref. 17). Force field calculations are in line with this picture (ref. 17). Attack from the "front" side does in fact lead to non-chelation control.

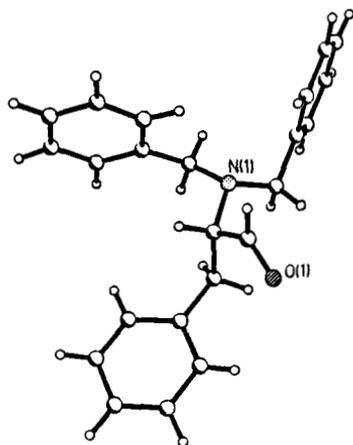
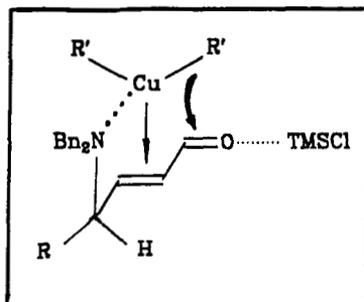
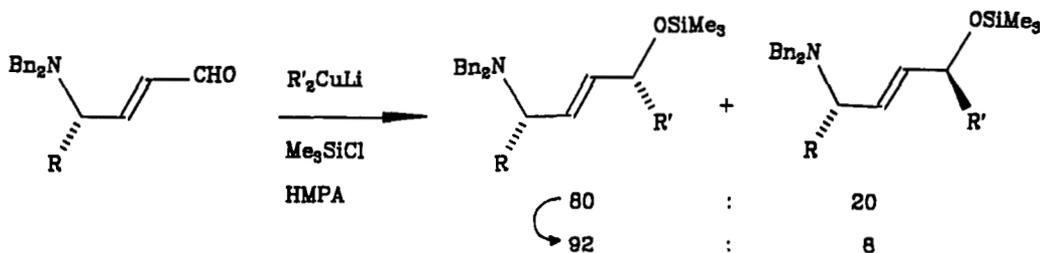


Fig. 3. X-ray structure of N,N-dibenzyl-phenylalaninal

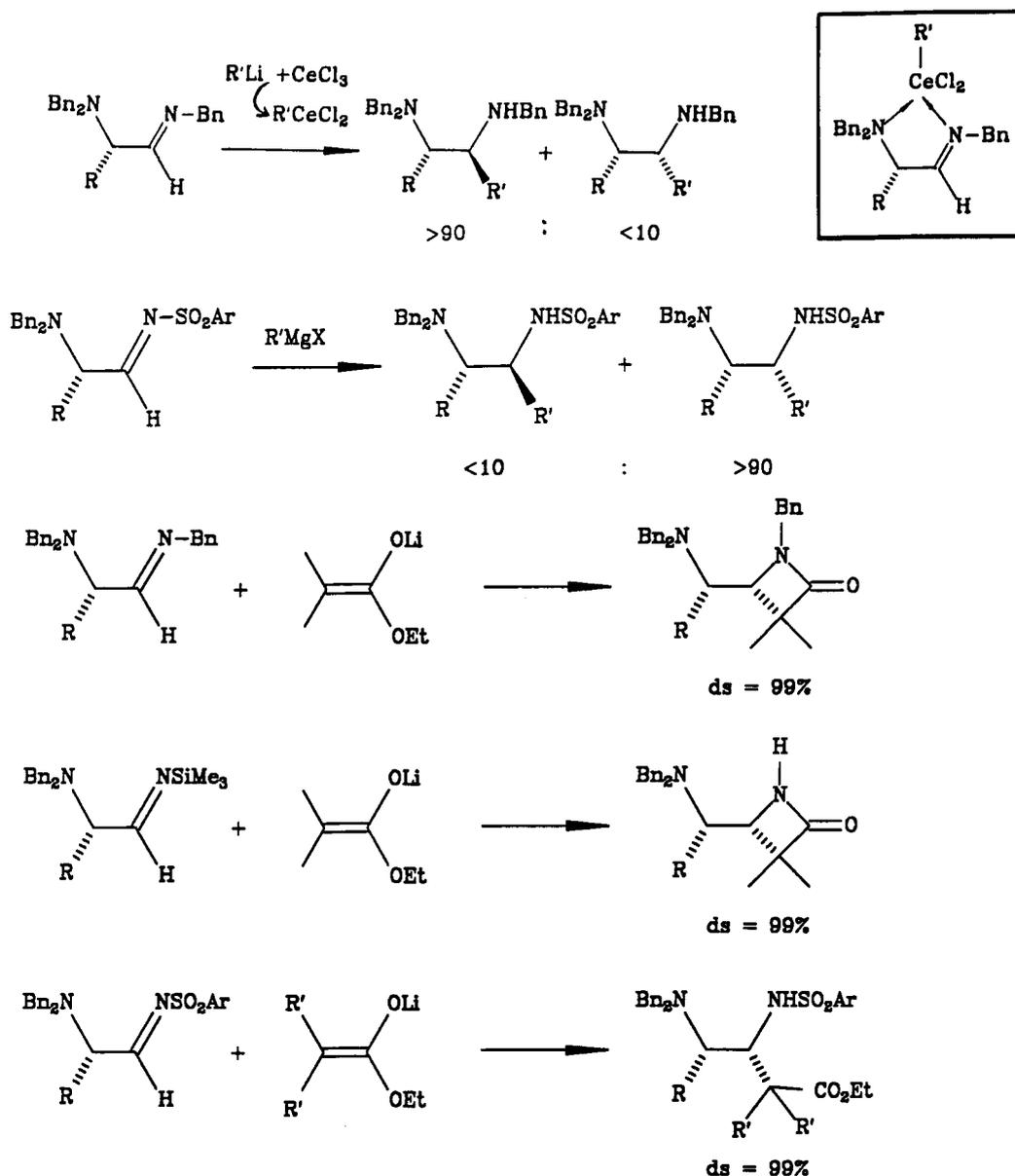
This model predicts that stereoselectivity should decrease if the protective groups are smaller, and increase if they are larger. This is observed experimentally (ref. 17,26). Reversing the sense of diastereoselectivity using chelating organometallics is not always efficient due to steric inhibition of chelation (ref. 17,20,23). However, the use of small protective groups in combination with cuprates results in high levels of chelation control (ref. 17,20).

The vinylogous forms of the aldehydes react with RLi , RMgX and RTiX_3 to deliver 1 : 1 mixtures of adducts. Surprisingly, cuprates in the presence of $\text{Me}_3\text{SiCl}/\text{HMPA}$ react in a 1,2-manner, stereoselectivity being $>82\%$ (ref. 27). This unusual remote asymmetric induction can be explained on the basis of diastereoselective π -complexation followed by a stereoselective walk to the π -terminus.



α -Amino aldimines

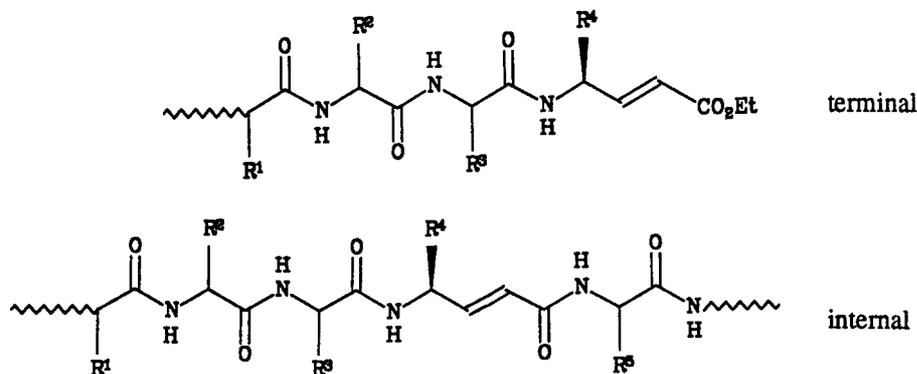
Grignard-type additions to aliphatic aldimines are notoriously difficult due to undesired α -deprotonation. However, we discovered that organocerium reagents add smoothly and under chelation control (ref. 28). In order to invert the sense of diastereoselectivity, we reasoned that electron-withdrawing protective groups are necessary. Indeed, the use of sulfonyl groups in combination with RMgX results in non-chelation controlled addition (ref. 28,29). Here again the power of protective group tuning is apparent.

**Electron-poor γ -aminoolefins**

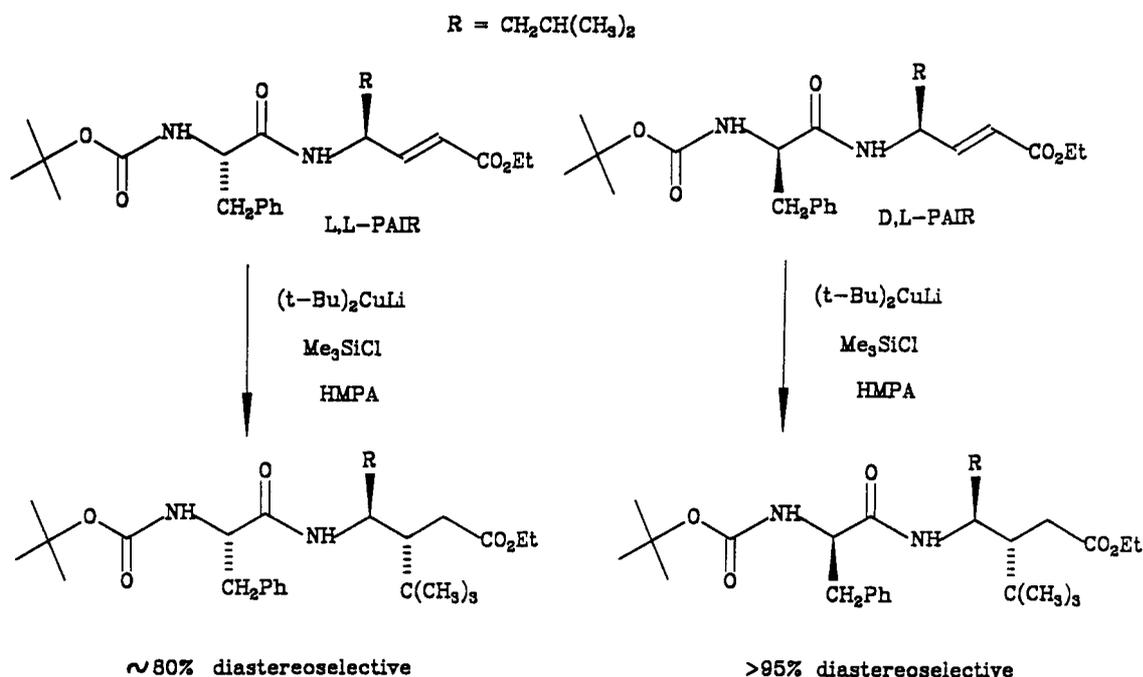
The α -amino aldehydes are easily converted into Wittig-Horner olefination products or Knoevenagel products (ref. 30). These react diastereoselectively with cuprates to form the syn- and anti-adducts, respectively.



In a related project we posed the question whether peptides incorporating α,β -unsaturated carbonyl moieties can be induced to undergo stereoselective cuprate, Michael and Diels-Alder additions (ref. 31). Either terminal or internal cases can be envisaged. In both cases 1,2-asymmetric induction may be expected to be the decisive factor. However, 1,n-asymmetric induction arising from remote centers could also play a role.



As the simplest possible starting point we chose dipeptides and synthesized several L,L- and D,L-pairs. In the case of the L,L-pair the best diastereoselectivity was observed with the bulky cuprate $(t\text{Bu})_2\text{CuLi}$ in the presence of $\text{Me}_3\text{SiCl}/\text{HMPA}$, but the 4 : 1 ratio of diastereomers could not be improved on. In contrast, the D,L-pair led to a single diastereomer!



The results seem to be general, since other L,L- and D,L-pairs show the same pattern of selectivity. Thus, 1,5-asymmetric induction appears to be as important as 1,2-asymmetric induction. At this point we speculate that the NH-acidic positions are metalated and that some sort of folding via chelation may place the remote stereogenic center near the reactive Michael acceptor. Alternatively, a rigid stretched conformation could also explain the results. It remains to be seen how larger peptides behave in these and other intriguing C-C-bond forming reactions.

Acknowledgement

This work was supported by the DFG (Leibniz-Programm and SFB 260) and the Fonds der Chemischen Industrie.

REFERENCES

1. M.T. Reetz, J. Westermann and R. Steinbach, Angew. Chem. **92**, 931 (1980); Angew. Chem. Int. Ed. Engl. **19**, 900 (1980); M.T. Reetz, J. Westermann and R. Steinbach, Angew. Chem. **92**, 933 (1980); Angew. Chem. Int. Ed. Engl. **19**, 901 (1980); M.T. Reetz, R. Steinbach, J. Westermann and R. Peter, Angew. Chem. **92**, 1044 (1980); Angew. Chem. Int. Ed. Engl. **19**, 1011 (1980).
2. M.T. Reetz, Top. Curr. Chem. **106**, 1 (1987); M.T. Reetz, Organotitanium Reagents in Organic Synthesis, Springer, Berlin 1986; see also B. Weidmann and D. Seebach, Angew. Chem. **95**, 12 (1983); Angew. Chem. Int. Ed. Engl. **22**, 31 (1983).
3. Review of chelation and non-chelation controlled reactions of alkoxy carbonyl compounds: M.T. Reetz, Angew. Chem. **96**, 547 (1984); Angew. Chem. Int. Ed. Engl. **23**, 556 (1984).
4. M.T. Reetz, R. Steinbach, J. Westermann, R. Peter and B. Wenderoth, Chem. Ber. **118**, 1441 (1985).
5. See for example: R.O. Duthaler, P. Herold, S. Wyler-Helfer and M. Riediker, Helv. Chim. Acta **73**, 659 (1990), and lit. cited therein.
6. See for example: T. Kauffmann, C. Pahde and D. Wingbermhühle, Tetrahedron Lett. **26**, 4059 (1985); G.A. Molander, E.R. Burkhardt and P. Weinig, J. Org. Chem. **55**, 4990 (1990).
7. T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, J. Am. Chem. Soc. **111**, 4392 (1989).
8. M.T. Reetz and J. Binder, Tetrahedron Lett. **30**, 5425 (1989).
9. L.E. Overman and R.J. McCready, Tetrahedron Lett. **23**, 2355 (1982); T. Nakata, T. Tanaka and T. Oishi, Tetrahedron Lett. **24**, 2653 (1983).
10. J.H. Morrison and H.S. Mosher, Asymmetric Organic Reactions, Prentice-Hall, New York 1971.
11. E.C. Ashby and J.T. Laemmle, Chem. Rev. **75**, 521 (1975).
12. M.T. Reetz, N. Harmat and R. Mahrwald, in preparation.
13. M.T. Reetz and R. Mahrwald, unpublished.
14. In carbohydrate chemistry the nature of the protective group plays a role in certain reactions; see also ref. 3 and 9.
15. X. Chen, E.R. Hortelano, E.L. Eliel and S.V. Frye, J. Am. Chem. Soc. **112**, 6130 (1990).
16. M.T. Reetz and M. Hüllmann, J. Chem. Soc., Chem. Commun. **1986**, 1600.
17. Review of amino acids as chiral building blocks: M.T. Reetz, Angew. Chem., in press (December issue 1991).
18. J. Jurczak and A. Golebiowski, Chem. Rev. **89**, 149 (1989).
19. BOC-protected serinal reacts stereoselectively with organometallics, but some racemization has been reported: P. Garner and J.M. Park, J. Org. Chem. **52**, 2361 (1987); P. Herold, Helv. Chim. Acta **71**, 354 (1988).
20. M.T. Reetz, M.W. Drewes and A. Schmitz, Angew. Chem. **99**, 1186 (1987); Angew. Chem. Int. Ed. Engl. **26**, 1141 (1987).
21. M.T. Reetz, Pure Appl. Chem. **60**, 1607 (1988).
22. M.T. Reetz, A. Schmitz and X. Holdgrün, Tetrahedron Lett. **30**, 5421 (1989).
23. M.T. Reetz, M.W. Drewes, K. Harms and W. Reif, Tetrahedron Lett. **29**, 3295 (1988).
24. See for example: S. Kano, T. Yokomatsu and S. Shibuya, Tetrahedron Lett. **32**, 233 (1991); M.M. Midland and M.M. Alfonso, J. Am. Chem. Soc. **111**, 4368 (1989); J. Jurczak, A. Golebiowski and J. Raczko, J. Org. Chem. **54**, 2495 (1989); P. Tebben, M. Reggelin and D. Hoppe, Tetrahedron Lett. **30**, 2919 (1989).
25. MO-calculations show that α -amino groups (in contrast to chloro groups) do not lower the LUMO of the carbonyl function significantly. However, if a Lewis acid complexes at the amino group, significant effects arise (ref. 17).
26. R.P. Bonar-Law, A.P. Davis, B.J. Dorgan, M.T. Reetz and A. Wehrsig, Tetrahedron Lett. **31**, 6725 (1990); M.T. Reetz and A. Wehrsig, unpublished.
27. M.T. Reetz, F. Wang and K. Harms, J. Chem. Soc., Chem. Commun. **1991**, 1309; the problem of vinylogous Cram-selectivity was addressed by Fleming: I. Fleming, H. Kühne and K. Takaki, J. Chem. Soc., Perkin Trans. I, **1986**, 725.
28. M.T. Reetz, R. Jaeger, R. Drewlies and M. Hübel, Angew. Chem. **103**, 76 (1991); Angew. Chem. Int. Ed. Engl. **30**, 103 (1991).
29. M.T. Reetz and M. Hübel, unpublished.
30. M.T. Reetz and D. Röhrig, Angew. Chem. **101**, 1732 (1989); Angew. Chem. Int. Ed. Engl. **28**, 1706 (1989).
31. M.T. Reetz and J. Kanand, unpublished.