Pure & Appl. Chem., Vol. 63, No. 11, pp. 1591–1598, 1991.
Printed in Great Britain.

Asymmetric synthesis and Cram's (chelate) rule

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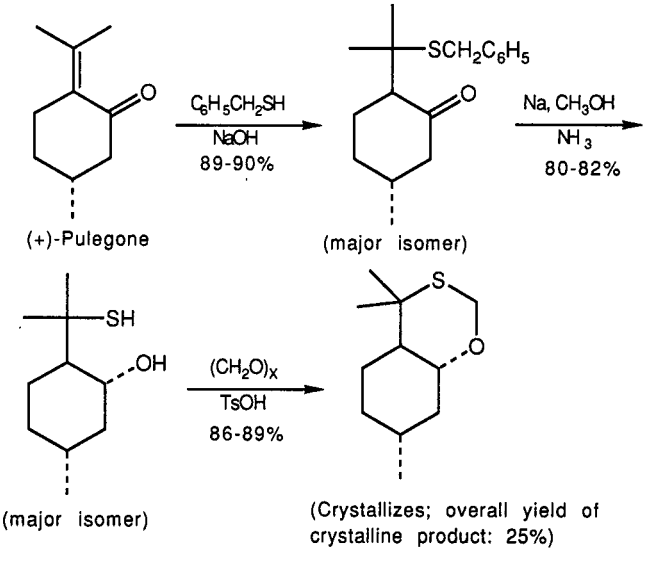
ABSTRACT

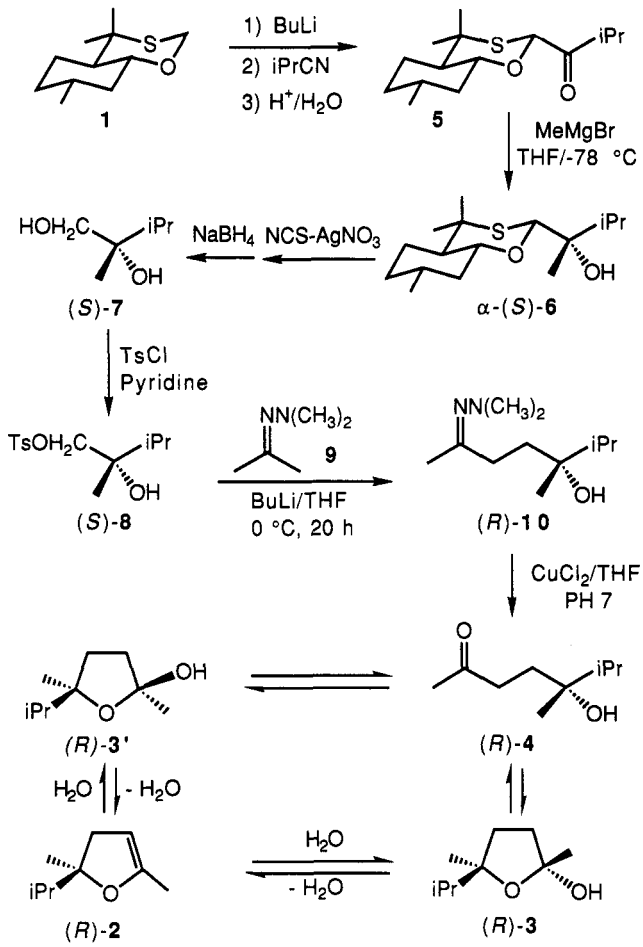
The asymmetric synthesis based on a chiral 1,3-oxathiane developed some years ago (ref. 1,4) has been applied (ref. 6) to an efficient synthesis of the sex attractant pheromone of the bark beetle *hyelocoetus dermestoides L.*, *(R)*-2,3-dihydro-2,5-dimethyl-2-isopropylfuran (Scheme 1). This work raised the question as to whether the intermediacy of chelates in Cram's "chelate rule" (ref. 15) is real. This question was answered (ref. 23) in the affirmative by kinetic and stereochemical studies of the reaction $C_2H_5COCH(R)CH_3 + (CH_3)_2Mg$. The rate of this bimolecular reaction was measured by rapid injection nmr (ref. 24) and it was found for a variety of R's [OSi(iPr)3, $OSi(C_6H_5)_2t$-Bu, $OSiMe_2t$-Bu, $OSiEt_3$, $OSiMe_3$, OCH_3] that stereoselectivity parallels rate qualitatively and quantitatively, with the non-chelating (ref. 17) OSi(iPr)3 derivative reacting slowest (and at the same rate as propiophenone, R = H) and the chelating OCH_3 compound reacting ca. 2000 times faster. The results are interpreted in terms of a competition between a non-chelating and a highly organized chelating transition state, with the $R=OCH_3$ compound - which chelates extensively - reacting fastest and with over 99% stereoselectivity giving the Cram product.

Some years ago we developed a method of enantioselective synthesis of tertiary (ref. 1) and secondary (ref. 2) hydroxyaldehydes, RR'C(OH)CHO (R = alkyl or H) which have served as synthons for a variety of chiral, nearly enantiomerically pure target molecules. The chiral auxiliary in this method is the oxathiane **1** derived from naturally occurring enantiomerically pure (+)-pulegone (Scheme 1) (ref. 3). Two earlier reviews (ref. 4) as well as a number of more recent publications (ref. 5) have dealt with this synthesis.

Scheme 1



Scheme 2



A typical example is the synthesis (ref. 6) of (*R*)-2,3-dihydro-2,5-dimethyl-2-isopropylfuran (**2**), the sex pheromone of the female beetle *hyelocoetus dermestoides L.* (Scheme 2). The structure and configuration of this compound was known from earlier work (refs. 7,8) and it had been synthesized before by lengthy routes in overall yields of 12% or less (refs. 7-9). There is uncertainty about the exact nature of the pheromone which is believed to be **2**; however, in presence of traces of moisture **2** is readily converted to a mixture of **3**, **3'** and **4** (Scheme 2).

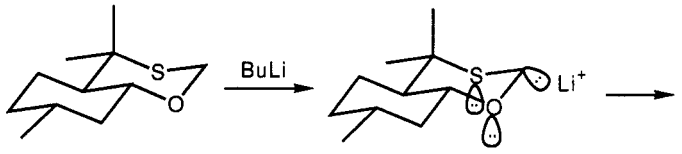
In the present work (ref. 6) compound **2** was synthesized in overall yield of 25% (Scheme 2) starting with **5**. The preparation of **5** from **1** involved a new method: treatment of nitriles with the lithium derivative of **1** (ref. 10). Although in this particular instance the diastereomer excess (d.e.) in the Grignard addition step leading to α-(*S*)-**6** is somewhat low [80% corresponding to a ratio of 9:1 of α-(*S*)-**6** to α-(*R*)-**6**], the d.e. can be readily increased to 96% by flash chromatography with an overall yield of α-(*S*)-**6** of 77%.

Cleavage of **6** to give alcohol (*S*)-**7** was effected with N-chlorosuccinimide - silver nitrate (ref. 11a) followed by *in situ* reduction with sodium borohydride. The other product of this cleavage is a cyclic sulfite (sultine) (ref. 1) which regenerates the chiral auxiliary **1** upon reduction with lithium aluminum hydride followed by reaction with paraformaldehyde and acid.

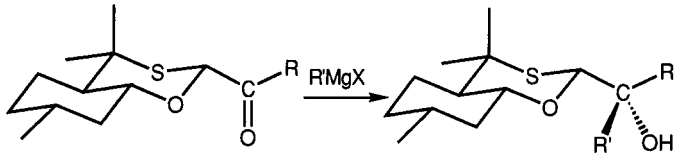
Intermediate (*S*)-**7** is converted to tosylate (*S*)-**8** which is used to alkylate acetone dimethylhydrazone **9** (ref. 11b). The product, (*R*)-**10** is immediately hydrolyzed by means of copper chloride (ref. 11b) to give ketone (*R*)-**4** which cyclizes spontaneously to hemiketals (*R*)-**3** and (*R*)-**3'**. Careful examination of the ^{13}C nmr spectrum of the product reveals a ratio of **4**:**3**:**3'** of 1:2:2 (in benzene-d_6 as solvent). The enantiomer excess, determined by

integration, in presence of Pr(hfc)3, of the ^{13}C signals at 82.9 and 82.7 ppm is 96±4%, equal to the diasteromer excess of the precursor **6**. Pyrolysis of **3/3'/4** either in the heated inlet chamber of a mass spectrometer or in the injection port of a gas chromatograph (temperature 250-300°C) produces **2**, whose ^{13}C nmr and mass spectra are identical with those reported by Mori (ref. 9).

Scheme 3



The equatrial carbanion is more stable because of more favorable disposition of the filled orbitals on S, O and C-2

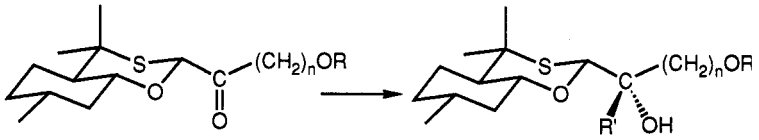


The reaction follows Cram's chelate rule (see Scheme 5)

It is of interest to discuss the reasons for the high stereoselectivity in the two salient steps of the synthesis: conversion of **1** to **5** and conversion of **5** to **6** (Scheme 3). In the first step, chirality is transferred from the existing chiral centers of the oxathiane (whose conformation is fixed by the ring fusion) to the new center at C-2. The rationale for the high stereoselectivity of the electrophilic substituion involved in this step has been previously discussed (refs. 12,13). The disposition of the filled orbitals on sulfur, oxygen and C-2 is such that the equatorial carbanion at C-2 is greatly preferred over the axial; the subsequent electrophilic substitution occurs with retention of configuration (ref. 14). The stereochemical course of the second step follows Cram's cyclic rule (see Scheme 5 below) which fixes the configuration of the new chiral center C-α, presumably through intervention of a chelate intermediate (ref. 15,16).

When we tried to apply this technique to ketones functionalized by a benzyl ether (OBn) group in the side chain (ref. 17) at positions α, β, γ or δ with the aim of obtaining triply functionalized molecules of the type $HO(CH_2)_nC(R)(OH)CHO$, we were seriously disappointed (see Scheme 4, entries 1,3,5 and 6). Especially with n = 1 or 2 (entries 1,3) stereoselectivity is nearly totally lost.

Scheme 4

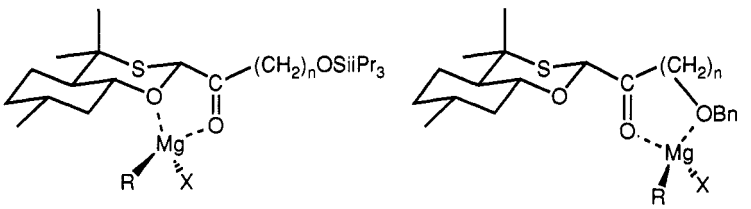


No	n	R	Reagent	d.e.[a]
1	1	$PhCH_2$	MeMgBr	-33
2	1	iPr_3Si	MeMgBr	95
3	2	$PhCH_2$	MeMgBr	-17
4	2	iPr_3Si	MeMgBr	95
5	3	$PhCH_2$	MeMgBr	62
6	4	$PhCH_2$	MeMgBr	77
7	2	Ph_3C	MeMgBr	72
8	2	$PhCH_2$	$LiBsBu_3H$	9
9	2	iPr_3Si	$LiBsBu_3H$	76
10	2	$PhCH_2$	iBu_2AlH	-66
11	2	iPr_3Si	iBu_2AlH	-77

a Diastereomeric excess. A negative sign implies that the major product is *not* that predicted by Cram's chelate rule

We surmised that this was due to competing chelation (Scheme 5) which interferes with chelation to the oxygen of the oxathiane ring that is normally responsible for the high stereoselectivity. This hypothesis is so much the more plausible in that stereoselectivity is partially restored when n = 3 or 4 (entries 5,6). In these cases the competing chelates (Scheme 5) involve 7- or 8-membered rings which are not favored; thus chelation to the oxathiane oxygen is partially regained. For the same reason, when the ether group is Ph_3C (entry 7, n = 2) steric factors suppress its competing chelation and stereoselectivity is again partially restored.

Scheme 5



When these results were presented in a lecture in Mexico City, Dr. Muchowski (Syntex) suggested to us protection of the alcohol function in the side chain by the triisopropylsilyl ["TIPS", (i-Pr)3Si] group which in other work had proved to be very bulky. The result (Scheme 4, entries 2,4) was almost magic: chelation with the side chain was apparently entirely prevented and complete stereoselectivity in the addition of the Grignard reagent to the ketone was regained! This is true also in the reduction with L-Selectride® LiB(sec-Bu)3H (entries 9 vs. 8). Normal stereoselectivity (with no functional group in the side chain) in such cases corresponds to a d.e. of about 80% (ref. 2) which, however, is completely lost when there is a benzyl ether function in the side chain (entry 8). However, reductions with DIBAL, [(*i*-Bu)2AlH, diisobutylaluminum hydride] proceed contrary to Cram's chelate rule both when R = Bn and when R = TIPS (entries 10,11). We believe that with this reagent no chelation occurs, since chelation would require pentacoordination of aluminum which is not favorable. This negative evidence strengthens the argument that the difference between OBn and O-TIPS substituents is, indeed, due to the fact that the former chelates and the latter does not.

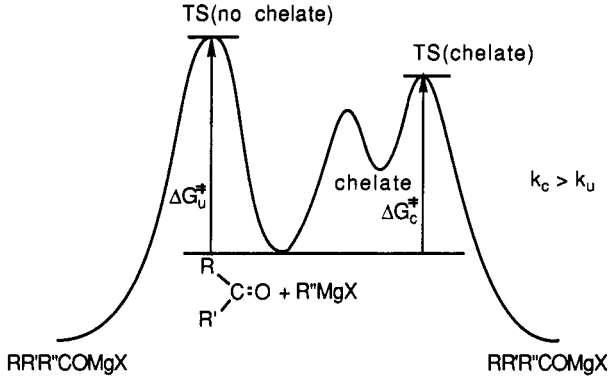
The outcome of these experiments prompted us to undertake an investigation of the basis of Cram's chelate rule. Chelation was postulated over 30 years ago (ref. 15) to be responsible for the high stereoselectivity observed in additions of organometallics to α-alkoxyketones and similar compounds. However, although there are many examples in the literature (ref. 16), often involving high stereochemical control, there is no mechanistic proof that chelates are, in fact, intermediates. Chelates have indeed been isolated in "static" experiments (i.e. where there is no nucleophilic addition to the ketone), for example with $MgBr_2$ in chloroform (ref. 18) and with titanium derivatives (ref. 19); in the latter case it was also shown (ref. 20) that the chelate is formed, and then disappears, with reagents that eventually add to the ketone. But, as had already been recognized by Ashby *et.al.* (ref. 21), these findings do not constitute proof that the chelate is an intermediate in the addition reaction; instead of being a true intermediate (route i) it may be a side product in equilibrium with the ketone (route ii):

$$\text{Reagents} \rightleftharpoons \text{Chelate} \rightarrow \text{Product} \qquad \text{(i)}$$
$$\text{Chelate} \rightleftharpoons \text{Reagents} \rightarrow \text{Product} \qquad \text{(ii)}$$

The only way to distinguish between these two reaction schemes is by kinetics: for pathway (i) chelation must accelerate the addition (cf. Scheme 6) but in case (ii) the reaction is slowed down because part of the starting ketone is sequestered as chelate. (*A priori*, the energy level of the chelate may be below that of the starting material; this would not affect the qualitative argument. However, quantitative experiments to be disucssed below as well as the very low concentration of static chelates in the strongly coordinating THF solvent militate against this possibility.) (ref. 23b).

Following Scheme 6 and equation (i) chelate formation, if indeed it leads to a reaction intermediate, must accelerate the reaction. There are two difficulties in demonstrating such acceleration. One stems from the need to compare reaction rates in the presence and in the absence of chelate formation: What is the proper species to compare with an α-alkoxyketone (which allegedly chelates)? Comparison with a similar ketone devoid of the α-alkoxy group may be inappropriate since the α-alkoxy substituent may affect the reaction rate other than by chelation (e.g. by an inductive effect). Evidently one must compare two very similar reactants, one that can chelate and the other than cannot do so. The earlier experiments described above provided the clue: $RCOCH_2OR'$ (R' = Bn or Me) will chelate, but the corresponding ketone with R' = TIPS will not. Therefore we decided to compare CH_3COCH_2OBn with CH_3COCH_2OTIPS as well as with $CH_3COCH_2CH_2CH_2CH_3$.

Scheme 6 The reaction will proceed via a chelated transition state (TS) only if the corresponding activation energy ($\Delta G_c^{\neq}$) is less than that ($\Delta G_u^{\neq}$) for the unchelated transition state; i.e. $k_c > k_u$.



The second difficulty relates to the fact that additions of organometallics to ketones are generally very fast. For this reason we used (ref. 22, 23) rapid injection nmr ("'RINMR"), developed by McGarrity (ref. 24), as a stop-flow kinetic method with nmr detection. The reagent chosen was $(CH_3)_2Mg$, in order to avoid the Schlenk equilibrium $2MeMgX \rightleftharpoons Me_2Mg + MgX_2$. Only one of the methyl groups of Me_2Mg reacts rapidly (ref. 21) and the reaction was followed by observing the disappearance of the methyl signal of this species (which differs from the signal of MeMgOR) in the nmr. (These two signals are upfield of all the others.) Thus it was found (refs. 22,23b) that CH_3COCH_2OBn reacts 140 times as fast as CH_3COCH_2OTIPS at -70°C whereas the TIPS compound reacts at about the same rate as $CH_3COCH_2CH_2CH_2CH_3$. Thus chelation leads to substantial rate acceleration whereas the inductive effect does not. Although the reaction of the benzyl ether is very fast (the half-life under pseudounimolecular reaction conditions was about 12 sec at -70°C) we were able to measure its specific reaction rate as well as that of the TIPS analog at two temperatures and thus were able to determine that the rate ratio at room temperature OBn/OTIPS is 11. Moreover we were able to confirm that the reaction is first order in Me_2Mg as had already been established for simple ketones by Ashby *et. al.* (ref. 21). This means that the same Me_2Mg molecule which complexes or chelates with the ketone is also the one that transfers the methyl group to the carbonyl carbon, in an intramolecular mechanism.

After proving that chelation of an α-alkoxy group greatly accelerates the reaction of a ketone with Me_2Mg it was left to show that there is a corresponding enhancement of stereoselectivity when there is a chiral center α to the ketone function. To this end we studied addition of Me_2Mg to ketones $PhCOCH(OR)CH_3$ where R = Me, Me_3Si, Et_3Si, *t*-$BuMe_2Si$, *t*-$BuPh_2Si$, (*i*-Pr)$_3Si$ (TIPS) and absent altogether, as in $PhCOCH_2CH_3$ (ref. 23). The specific reaction rate was determined by RINMR as before and the diastereomeric products were analyzed by

proton nmr. (Preparative additions were carried out at -78°C whereas the kinetic experiments were done at -70°C.) The results are shown in Table 1.

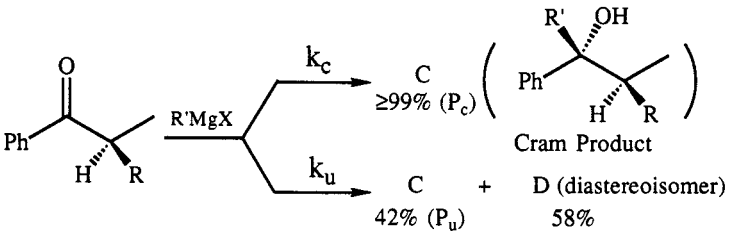
TABLE 1

Ketone	R	Rate Constant $k_2(x10^2M^{-1}s^{-1})$	% C Exp[a]	% C Calc[b]
1	OMe	~1000	>99	(100)
2	$OSiMe_3$	100 ± 30	99	99.7±0.1
3	$OSiEt_3$	7.9 ± 1.0	96	96.7±0.7
4	$OSitBuMe_2$	2.5 ± 0.3	88	89±2
5	$OSitBuPh_2$	0.82 ± 0.06	63	68±5
6	$OSi(iPr)_3$	0.45 ± 0.04	42	(42)
7	H	0.54 ± 0.06	-	-

a. Experimental b. Calculated

It is immediately evident that, as the rate constants increase, the stereoselectivity of the reaction increases also along the series R = TIPS < *t*-BuPh2Si < *t*-BuMe2Si < Et3Si < Me3Si < Me. The TIPS ether reacts at the same rate as propiophenone itself, showing once more that the inductive effect of the O-TIPS group is not important. In the case of the TIPS ether only, the predominant product is not the "Cram product" C (formed only to the extent of 42%) but its diastereomer D (58%) (Scheme 7). With the other silyl ethers, as the rate constants increase there is an increasing amount of the chelate product C. With Me3Si the rate constant is already 200 times larger than with

Scheme 7



TIPS and the diastereomer ratio is about 99:1. At even larger ratio (product D not seen) is found with the methyl ether which reacted too fast to measure by stop flow kinetics. Its reaction velocity was determined by allowing it and the trimethylsilyl ether to compete for a limited amount of Me2Mg and measuring the product ratio: it reacts about 10 times as fast as the trimethylsilyl ether.

Thus a clear correlation between specific reaction rate and stereoselectivity is established, and since it was known from the earlier work (ref. 22) (see Scheme 6) that rate increases when there is chelation, it follows that stereoselectivity also runs parallel with chelation. Thus the mechanistic base for Cram's chelate rule is put on a firm footing (ref. 23).

Mechanistic arguments are always more convincing when they rest on a quantitative basis. If one asumes that some of the siloxylated ketones – those in which the silyl group is *t*-BuPh2Si, *t*-BuMe2Si , Et3Si, Me3Si – react in part via a chelated and in part via an unchelated transition state (i.e. that there is a partitioning of reaction paths), one arrives at the picture shown in Scheme 7. (See also Scheme 6 where it is now assumed that the transition

states are comparable in free energy, i.e. $\Delta G^{\neq}_C \sim \Delta G^{\neq}_U$.) The composition of the product mixture can then be calculated making the following assumptions:

1) The products obtained via the unchelated transition state always have the same composition: 42% "Cram" product (C) and 58% diastereomer D.
2) The rate constant for reaction via the unchelated transition state is always the same (k_U) and is equal to the rate constant for the TIPS ether, i.e. the nature of the ether moiety has no effect on k_U.
3) The experimental rate constant k_2 is the sum of k_U and k_C (the rate constant for the process involving chelation): $k_2 = k_C + k_U$. Thus the fraction of molecules passing through the chelated transition state is $k_C/k_2 = 1 - k_U/k_2$
4) That part of the reaction which passes through the chelated transition state gives exclusively the "Cram" product C. It then follows that

$$\%C = 42\,(k_U/k_2) + 100\,(1 - k_U/k_2) \qquad \text{(iii)}$$

Hence $$\%C = 100 - 58 \cdot k_U/k_2 \qquad \text{(iv)}$$

In the last column of Table 1 the observed product composition in each case is compared with that calculated by equation (iv) using the observed rate constants k_2 and k_U. Although the precision of the calculation is not very high (because of the large standard deviations in the rate constants; the stop-flow RINMR method is not very accurate), the calculated composition agrees with the experimental within the error limits. This justifies the simple picture presented in Schemes 6 and 8, i.e. partition between a direct reaction and one involving chelate intermediates, or at least a chelated transition state.

Finally it is noteworthy that the fastest reactions are also the most stereoselective. This is contrary to most chemists' intuition, according to which a large difference in diastereomeric transition states ($\Delta\Delta G^{\neq}$), i.e. high stereoselectivity, requires that the individual activation energies ($\Delta G^{\neq}$) for the two processes also be large. Clearly, this is not the case here; instead the situation resembles that found with enzyme-catalyzed reactions where fast reaction and high stereoselectivity often go hand-in-hand. With enzymes this is generally attributed to a highly organized transition state, which follows upon a high organized enzyme-substrate complex. Such high organization implies that the functional groups of the substrate are in the right place for reaction, which, in turn, leads to a high reaction rate. At the same time, the highly organized transition state is well disposed toward high stereoselectivity. An analogous situation may well be found in the case where Cram's chelate rule applies: the chelate is a highly organized intermediate leading to an equally organized transition state in which the nucleophile is well positioned to interact (rapidly) with one face of the carbonyl substrate (i.e. stereoselectively).

Acknowledgements This work was supported in part by the National Science Foundation (grant CHE-8703060) and by the Petroleum Research Fund, administered by the American Chemical Society (grant 17171-AC), to whose donors we are grateful. X.C. was supported by a Glaxo fellowship.

REFERENCES

1. J.E. Lynch and E.L. Eliel, *J. Am. Chem. Soc. 106*, 2943 (1984).
2. K.-Y. Ko, W.J. Frazee, and E.L. Eliel, *Tetrahedron , 40*, 1333 (1984).
3. E.L. Eliel, J.E. Lynch, F. Kume and S.V. Frye, *Org. Syntheses 65*, 215 (1987).
4. E.L. Eliel, Phosphorus and Sulfur *24*, 73 (1985); E.L. Eliel, J.K. Koskimies, B. Lohri, W.J. Frazee, S. Morris-Natschke, J.E. Lynch and K. Soai, in "*Asymmetric Reactions and Processes in Chemistry*" E.L. Eliel and S. Otsuka eds. p.37, Am. Chem. Soc., Washington, DC (1982).
5. S.V. Frye and E.L. Eliel, *Tetrahedron Lett. 26*, 3907 (1985). S.V. Frye and E.L. Eliel, *J. Org. Chem. 50*, 3402 (1985). S.V. Frye and E.L. Eliel, *Croat. Chim. Acta 58*, 647 (1985). M. Ohwa, T. Kogure and E.L. Eliel, *J. Org. Chem. 51*, 2599 (1986). K.-Y. Ko, and E.L. Eliel, *J. Org. Chem. 51*, 5353 (1986). M. Ohwa and E.L. Eliel, *Chem. Lett.* 41, (1987). E.L. Eliel, M.T. Alvarez and J.E. Lynch, *Nouv. J. Chim. 10*, 749 (1986). E.L. Eliel and J.E. Lynch, *Tetrahedron Lett. 28*, 4813 (1987). J. Kaulen, *Angew. Chem., Int. Ed. Engl. 28*, 462 (1989). H. Cervantes-Cuevas and P. Joseph-Nathan, *Tetrahedron Lett. 29*. 5535 (1988).

6. X. Bai and E.L. Eliel, *J. Org. Chem. 56*, 2086 (1991).
7. H. Redlich, X.-J. Jiang, H. Paulsen and W. Francke, *Tetrahedron Lett. 22*, 5043 (1981).
8. H. Redlich and X.-J. Jiang, *Liebigs Ann. Chem.* 717 (1982).
9. K. Mori, T. Ebata, and S. Takechi, *Tetrahedron 40*, 1761 (1984).
10. E.L. Eliel and X. Bai, *J. Org. Chem. 55*, 4951 (1990).
11. a) E.J. Corey and D. Enders, *Tetrahedron Lett.* 3 (1976); b) E.J. Corey and S. Knapp, *ibid.* 3667 (1976).
12. J.-M. Lehn and G. Wipff, *J. Am. Chem. Soc. 98*, 7489 (1976).
13. N.D. Epiotis, R.L. Yates, F. Bernardi and S. Wolfe, *J. Am. Chem. Soc. 98*, 5435 (1976).
14. D.J. Cram, *"Fundamentals of Carbanion Chemistry"* Academic Press, New York, NY (1965).
15. D.J. Cram and K.R. Kopecky, *J. Am. Chem. Soc. 81*, 2748 (1959).
16. E.L. Eliel in J.D. Morrison, ed. *"Asymmetric Synthesis" 2*, p.125, Academic Press, New York, NY (1983).
17. S.V. Frye and E.L. Eliel, *J. Am. Chem. Soc. 110*, 484 (1988).
18. G.E. Keck and S. Castellino, *J. Am. Chem. Soc. 108*, 3847 (1986).
19. M.T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth and R. Steinbach, *Angew. Chem. Suppl.* 1511 (1983).
20. M.T. Reetz, M. Hullman and T. Seitz, *Angew. Chem. Int. Ed. Engl. 26*, 477 (1987).
21. J. Laemmle, E.C. Ashby and H.M.J. Neumann, *J. Am. Chem. Soc. 93*, 5120 (1971).
22. S.V. Frye, E.L. Eliel and R.J. Cloux, *J. Am. Chem. Soc. 109*, 1862 (1987).
23. a) X. Chen, E.R. Hortelano, E.L. Eliel and S.V. Frye, *J. Am. Chem. Soc. 112*, 6130 (1990); b) *id*, manuscript submitted.
24. J.F. McGarrity, *Org. Magn. Reson. 17*, 59 (1981).