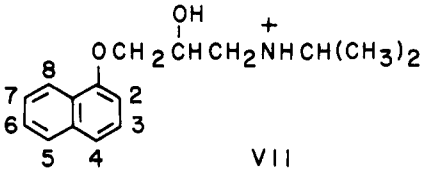
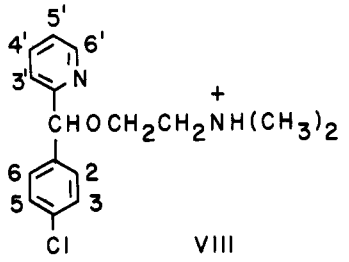
thanide shift reagents for cations have been described,[35] although most applications of these have been with metal ions of physiological importance such as sodium, potassium, calcium, and magnesium. It is generally noted that lanthanide complexes of tripolyphosphate or triethylenetetraaminehexaacetic acid [Ln(TTHA)$^{3-}$] are the best shift reagents for cations.[35] The spectra of propranolol hydrochloride (VII) and carbinoxamine maleate (VIII) exhibited shifts in the presence of lanthanide complexes of TTHA.



VII



VIII

Broadening in these spectra was minimal at 300 MHz, indicating that the association between the shift reagent and substrate were fast on the NMR time scale. Improvements in the ability to measure enantiomeric resolution in the spectra of these two compounds with either β- or γ-cyclodextrin were realized on adding complexes of the formula Ln(TTHA)$^{3-}$.

Enantiomeric resolution in the spectrum of propranolol hydrochloride is better with γ-cyclodextrin than β-cyclodextrin.[23] The slight resolution of H_8 and H_2 observed in solutions of γ-cyclodextrin (0.030 M) and propranolol hydrochloride (0.030 M) was enhanced on addition of Pr(TTHA)$^{3-}$ (0.0075 M). The complicated aromatic portion of the spectrum from 7.3 to 7.6 ppm containing the resonances for H_3, H_4, H_6, and H_7 was altered as the concentration of Pr(TTHA)$^{3-}$ was raised from 0.0075 to 0.0900 M. At the higher value of shift reagent, the resonance corresponding to H_7 was resolved from the other signals and seen to exhibit enantiomeric resolution of 8.2 Hz.

Enantiomeric resolution has been observed for several resonances in the spectrum of carbinoxamine maleate with β-cyclodextrin.[24] The resolution was better, however, when γ-cyclodextrin was employed as the resolving agent. In solutions of carbinoxamine maleate (0.025 M) and γ-cyclodextrin (0.025 M), the resonance of the benzylic hydrogen changed from one to two singlets, with enantiomeric resolution of 7.1 Hz. Enantiomeric resolution was also evident in the resonances for H_3' (2.7 Hz), $H_{3,5}$ (2.8 Hz), and $H_{2,6}$ (2.8 Hz). Addition of Yb(TTHA)$^{3-}$ (0.025 M) improved the enantiomeric resolution of $H_{3,5}$ and $H_{2,6}$ to 3.8 Hz. Addition of Pr(III)nitrate caused slight shifts in the spectrum of carbinoxamine maleate, perhaps through chelate association of Pr(III) at the pyridyl nitrogen and ether oxygen atoms. The enantiomeric resolution of the resonance of the benzylic hydrogen was enhanced by 1 Hz.

Provided one can identify a suitable achiral lanthanide shift reagent for a substrate, addition of a lanthanide species to mixtures of substrates with chiral resolution agents seems to generally improve enantiomeric resolution. This method is expected to work effectively with soluble analogues of the wide variety of chiral donor–acceptor and cavity liquid chromatographic stationary phases that have been described in the literature.

Acknowledgment. We wish to thank Research Corporation, the National Science Foundation (Research at Undergraduate Institution Program, CHE-8921335 and CHEM-9111778), and The Camille and Henry Dreyfus Foundation (Scholar/Fellow Program) for supporting this work.

Registry No. I, 69632-50-4; II, 86091-69-2; III, 69632-32-2; IV, 66964-32-7; (*R*)-V, 50691-97-9; (*S*)-V, 39200-48-1; (*R*)-VI, 51990-97-7; (*S*)-VI, 50691-96-8; (*R*)-methyl *p*-tolyl sulfoxide, 1519-39-7; (*S*)-methyl *p*-tolyl sulfoxide, 5056-07-5; (*R*)-methyl phenyl sulfoxide, 4850-71-9; (*S*)-methyl phenyl sulfoxide, 18453-46-8; β-cyclodextrin, 7585-39-9; γ-cyclodextrin, 17465-86-0.

(35) Chu, S. C.; Pike, M. M.; Fossel, E. T.; Smith, T. W.; Balschi, J. A.; Springer, C. S., Jr. *J. Magn. Reson.* **1984**, *56*, 33.

Enantioselective Formation of *cis*-3,5-Dimethylcyclohexanone Lithium Enolate and Stereoselective Aldol Reaction with Benzaldehyde

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Deprotonation of *cis*-3,5-dimethylcyclohexanone (**6**) with chiral lithium amide bases **10–12** has been investigated. The resulting lithium enolates **7a,b** react with benzaldehyde, acetic anhydride, or trimethylsilyl chloride to yield, respectively, the aldols **8** and **9**, the acetates **13a,b**, and the enol ethers **14a,b** as nonracemic mixtures in high yields and up to 79% ee. Effects of solvents and additives on the selectivity of these reactions have been studied. A model based on the hypothesis that the deprotonation of **6** with lithium amides proceeds via a pericyclic transition state involving a dimer of the base is proposed.

Deprotonation of a ketone followed by a reaction of the resulting enolate with an electrophile is one of the fundamental reaction sequences in organic synthesis. In the last decade this process has been the focus of vigorous investigations by several groups, and many of its salient features are now firmly established.[1] Complexation be-

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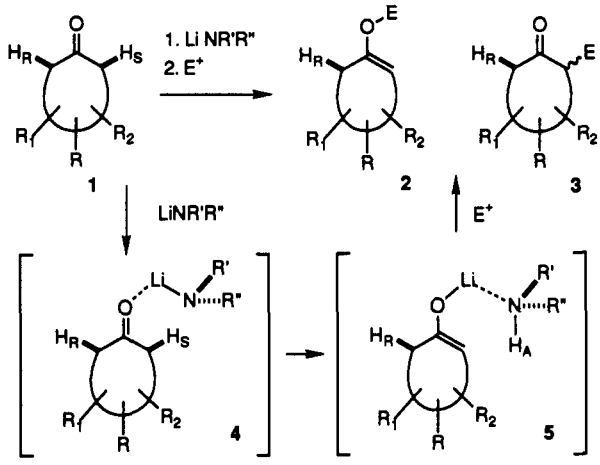
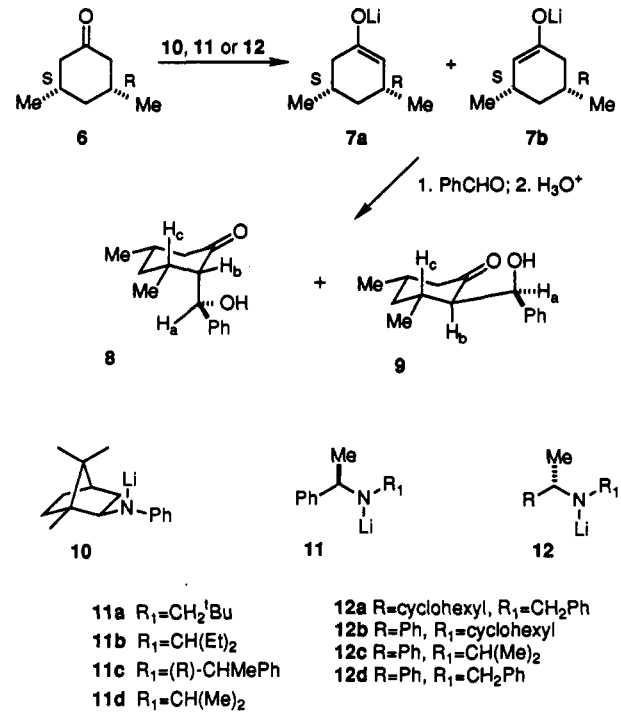
Scheme I



tween reactants is especially important in the synthesis of chiral, nonracemic materials, and the realization that the reaction of ketones with lithium amides most likely encompasses at least two interesting complexes, a ketone–lithium amide complex and an enolate–amine complex[2] (cf. 4 and 5[3]), provided a stimulus to investigating chiral lithium amides as reagents for the construction of chiral molecules via deprotonation.[4]

A general reaction which involves a cyclic ketone and leads to the chiral products 2 and/or 3 (Scheme I) can, in principle, adhere to one of the three scenarios: (i) Both the starting ketone 1 and the intermediate enolate are achiral (e.g., R, R_1, R_2 = H). (ii) The ketone 1 is achiral ($R_1 = R_2$, 1 has C_s symmetry) but the enolate is chiral. (iii) The ketone 1 is chiral. In the first case the use of a chiral lithium amide results in nonracemic products due to the influence of the chiral amine which is complexed to the enolate.[1i,4,5] Approaches based on the second scenario led, during the last 5 years, to the development of a new, promising synthetic strategy.[4,6] It should be noted that this strategy calls for efficient differentiation of two enantiotopic groups (hydrogens H_R and H_S), a process rare outside the realm of enzyme chemistry.[7] In the third case either two enantiomers of the racemic ketone 1 react with a chiral base LiNR′R″ at different rates[4,8] (kinetic resolution), or the chiral amine serves as the noncovalently bonded chiral auxiliary and the enolate displays stereotopic face selectivity.[4,9]

Scheme II



11a R_1=$CH_2{}^tBu$
11b R_1=$CH(Et)_2$
11c R_1=(R)-CHMePh
11d R_1=$CH(Me)_2$

12a R=cyclohexyl, R_1=CH_2Ph
12b R=Ph, R_1=cyclohexyl
12c R=Ph, R_1=$CH(Me)_2$
12d R=Ph, R_1=CH_2Ph

Table I. Summary of Aldol Experiments (Scheme II)

entry	base	yield[a] (%)	9:8	8 ee (%)	9 ee (%)
1	LDA	86	64:36		
2	**10**	76	63:37	11	3
3	**11a**	59	66:34	21	24
4	**11b**	50	63:37	32	34
5	**12a**	56	61:39	43	25
6	**12b**	61	66:34	51	30
7	**11c**	55	64:36	52	42
8	**12c**	42	63:37	52	41
9	**11d**	52	63:37	54	43
10	**12d**	51	60:40	57	51
11	**12d**[b]	45[a]	50:50[b]	74[b]	57[b]
12	**12d**[c]	42[c]	49:51[c]	61[c]	57[c]
13	**12c**[d]	61[d]	66:34[d]	53[d]	39[d]

[a] Isolated yield. [b] Experiment was carried out under "rapid quench" conditions. [c] Three quiv of LiBr was added to the enolate. [d] Longer reaction time (30 min).

As part of a study concerning reactions which proceed with enantiotopic group selectivity we investigated the deprotonation of *cis*-3,5-dimethylcyclohexanone (**6**) with chiral lithium amide bases **10**–**12** and the aldol reaction of the resulting enolates (Scheme II). The reaction was surprisingly diastereoselective and instead of a mixture of all four diastereoisomeric aldols only two isomers were obtained. The minor product was identified as the cis-threo isomer **8** and the major product as the trans-erythro isomer **9**[10] (Scheme II; only one enantiomer of each of the compounds **8** and **9** is shown). Six-membered endocyclic enolates usually show a small preference for axial attack during alkylation; this has been rationalized by stereoelectronic effects.[1e-g,k,6a] An equatorial alkyl group at the 3 position can, however, direct the alkylating agent to approach from the opposite face (resulting in the trans diequatorial product).[1f,k] Formation of the trans product **9** seems to indicate the same trend in the aldol addition reaction. Cyclic enolates are known to give mainly threo aldols; the slight predominance of the erythro isomer over

(1) For review, see inter alia: (a) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (d) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (e) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111. (f) Evans, D. A. *Ibid.* pp 1 and 51. (g) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Toronto, 1983; p 274. (h) Pollack, R. M. *Tetrahedron* **1989**, *45*, 4913. (i) Seebach, D. *Angew Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (j) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 2, p 181 and other chapters in this volume. (k) Caine, D. *Ibid.* Vol. 3, p 12.

(2) (a) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. (b) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(3) The structures 4 and 5 are schematic representations and do not take into account aggregation and solvation of reagents.

(4) Review: Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.

(5) (a) Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657. (b) Ando, A.; Shioiri, T. *Tetrahedron* **1989**, *45*, 4969.

(6) (a) Majewski, M.; Zheng, G.-Z. *Synlett* **1991**, 173. (b) Cox, P. J.; Simpkins, N. S. *Ibid.* **1991**, 321.

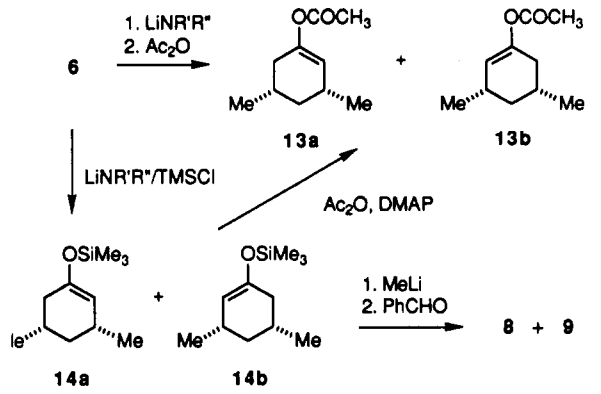
(7) Review: Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1.

(8) Coggins, R.; Simpkins, N. S. *Synlett* **1991**, 515.

(9) Sobukawa, M.; Nakajima, M.; Koga, K. *Tetrahedron: Asymmetry* **1990**, *1*, 295.

(10) For a general discussion of stereostructural notations used in aldol chemistry and methods of elucidating aldol structures see ref 1e, pp 112–118.

Scheme III



the threo one in our case is, presumably, a result of steric effects exerted by the methyl group at C-3.[11]

Deprotonation of **6** with chiral lithium amides **10–12** followed by treatment of the nonracemic mixture of the resulting chiral enolates with benzaldehyde gave optically active aldol products (Table I). The enantiomeric composition of these products was measured by NMR using the optically active shift reagent Eu(tfc)$_3$; the highest ee observed was 74%. Bases **12a–d** produced predominantly the 3*S*,5*R* isomer of the enolate **7b**[12] and subsequently the 3*S*,5*R* isomers of **8** and **9** as the major products. The use of bases **10** and **11a–d** resulted in enantiocomplementary results. In all cases the enolate was allowed to react with benzaldehyde only for a short time (2 min) to minimize possible interconversion of the products; the yields reported are, for that reason, not optimal. In one case it was established that when the reaction was allowed to proceed for a longer time (30 min) the yield increased significantly with negligible changes in the ratio of diastereoisomers and in the ee (cf. Table I, entry 13 vs 8). We also observed that the enolization of **6** with chiral lithium amides was measurably slower than the enolization with LDA.[13] The latter required typically 20–30 min at −78 °C, whereas when, for example, chiral base **11d** was used, stirring the mixture for 2 h at −78 °C was necessary for a reasonably complete enolization. However, when benzaldehyde was added to the reaction mixture 2–3 min after the addition of the ketone to the base, the reaction proceeded cleanly, there was no evidence of the reduction of the aldehyde with LDA (nor with any of the other amides),[14] and the yield was often higher than in cases where the lithium amide was allowed to react with the ketone for a long time prior to quenching the reaction with benzaldehyde. This technique, which we called the "rapid quench", resembles Corey's "internal quench" technique[15] and the results indicate that aromatic aldehydes are compatible with ketone–lithium amide mixtures, as opposed to lithium amide alone,[14] and that the enolization of ketones is faster in the presence of benzaldehyde. Both these phenomena might be due to ligation of benzaldehyde to an aggregated ketone–lithium amide complex.

Table II. Synthesis of the Acetates 13a,b (Scheme III)

entry	base	solvent (additive)	convn[a] (%)	yield[b] (%)	ee (%)
1	**12a**	THF		52	29
2	**11c**	THF		77	34
3	**12d**	THF	37	38	62
4	**12d**	hexane	40	20	39
5	**12d**	hexane (THF)[c]	41	26	40
6	**12d**[d]	THF	38	37	70[d]
7	**12c**	THF	88	79	53
8	**12c**[e]	THF	60	52	51[e]
9	**12c**[d]	THF	85	67	45[d]
10	**12c**	Et_2O	76	62	47
11	**12c**	hexane	71	44	30
12	**12c**	hexane (THF)[c]	80	58	48
13	**12c**	PhMe	71	29	30
14	**12c**	PhMe (THF)[c]	71	40	41
15	**12c**	THF (HMPA)[f]	59	42	35
16	**12c**	THF (HPMA)[g]	74	76	41
17	**12c**	THF (TMEDA)[f]	56	33	44
18	**12c**	PhMe (THF; LiBr)[h]	92	67	64

[a] Conversion of **6** to **13** measured by GC. [b] Isolated yield of **13**. [c] Four equiv of THF. [d] Two equiv of base was used. [e] 0.5 equiv of base was used. [f] Four equiv. [g] 0.5 equiv of HMPA. [h] Six equiv of THF and 1 equiv of LiBr.

Table III. Synthesis and Reactions of Silyl Enol Ethers 14a,b

entry	base	yield of 14[a,b] (convn %)[d]	deriv (yield,[a] %)	ee[c] (%) (comp)
1	LDA	53 (91)		
2	**12c**	58 (85)	aldol (88)[e]	77 (**8**); 61 (**9**)
3	**12d**	67 (91)	aldol (98)[e]	68 (**8**); 65 (**9**)
4	**12d**[f]	51 (67)	acetate (26)	79 (**13**)

[a] Isolated yield (%). [b] Corey's internal quench method was used to generate silyl enol ethers. [c] The ee was measured by NMR using Eu(hfc)$_3$ or Eu(tfc)$_3$. [d] Conversion rate of the ketone to the silyl enol ether measured by GLC. [e] Compounds **8** and **9** were produced in a ratio of 1:1. [f] This reaction was carried out at −100 °C; a similar reaction at −78 °C yielded the acetate in 74% ee.

To avoid complications associated with the presence of more than one diastereoisomeric product and with the possibility of interconversion of these products under the reaction conditions we turned to reactions in which the enolate reacts at the oxygen terminus. These reactions produce only one pair of enantiomeric products; silylation according to the "internal quench" technique has been proven to lead to best results as far as reactions of ketones of C_s symmetry are concerned.[4] In our system we were unable to find a technique which would allow us to measure the ee of nonracemic mixtures of the silyl enol ethers of ketone **6**. However, the acetate of this ketone was more amenable to the shift reagent NMR analysis. Deprotonation of **6** with the bases which gave the best results in the aldol series and quenching the resulting enolates with acetic anhydride (Scheme III) produced the results which are summarized in Table II.

The enantioselectivity of deprotonation–acetylation was very similar to the enantioselectivity of the deprotonation followed by the aldol reaction (cf. entries 5, 7, 8, and 10 in Table I and entries 1, 2, 7, and 3 in Table II, respectively). We wanted to evaluate the effect of solvents and additives on selectivity of the reaction. The solvent of choice turned out to be THF, since running the reaction in nonpolar solvents or in ether resulted in lower enan-

(11) (a) Selective formation of a *trans-erythro* aldol product from the Zn enolate of 3-methylcyclohexanone has been observed before: Heng, K. K.; Smith, R. A. J. *Tetrahedron* **1979**, *25*, 425. (b) In an effort to establish if compounds **8** and **9** undergo equilibration the following experiments were performed: A solution of pure aldol **8** (0.35 mmol) in THF (1.5 mL) was added to a solution of LDA (1.1 equiv) in THF (4 mL) at −78 °C. The mixture was stirred for 30 min and then was quenched with NH_4Cl. Extractive workup yielded pure **8** (86% yield). Analogous experiment with 91% pure **9** (the sample contained 9% of compound **8**) afforded a mixture of **8** and **9** in a ratio of 18:72 (90% yield).

(12) Absolute configurations of enolates and aldols were assigned by analogy to the results of Koga: Kim, H.; Shirai, R.; Kawasaki, H.; Nakajima, M.; Koga, K. *Heterocycles* **1990**, *30*, 307.

(13) (a) Simpkins observed an even slower deprotonation of *cis*-2,6-dimethylcyclohexanone: Cain, C. M.; Cousins, R. R. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523. (b) The rate of enolization was estimated by adding *n*-BuLi to mixtures of ketone with a lithium amide at different time intervals and, after quenching with water, measuring the ratio of the starting ketone to the *tert*-butylcarbinol by GC: Gleave, D. M. Unpublished observations.

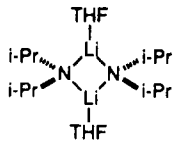
(14) Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 4057.

(15) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

tioselectivity (Table II, entries 3–5 and 7, 10, 11, 13). The presence of polar additives (HMPA, TMEDA) was also detrimental (cf. Table II entries 7, 15–17). And, finally, a reaction run in a nonpolar solvent in the presence of LiBr (conditions under which the formation of a mixed lithium amide–LiBr dimer analogous to **16**, vide infra, should be maximized) produced the acetate **13** in high conversion and with higher enantioselectivity than the reaction run under normal conditions (cf. Table II, entries 7 and 18).

Deprotonation of **6** with bases **12c** and **12d** in the presence of trimethylsilyl chloride led to the efficient formation of **14a** and **14b**. Purification of these volatile compounds resulted in some loss of material which was reflected in the yields. The nonracemic mixtures of **14a** and **14b** were converted into the aldol products **8** and **9** or into the acetate **13** in order to measure the ee. As observed in similar systems,[4] these compounds showed higher ee's than the aldols and acetates generated directly (cf. Table III, entries 2 and 4, Table I, entry 8, and Table II, entry 3, respectively).

Development of new synthetic strategies based on enantioselective deprotonation is greatly hindered by lack of understanding of the details of interactions between chiral lithium amides and cyclic ketones. In analyzing this process we found several observations difficult to rationalize: why do some of the lithium amides (e.g., **11d**) deprotonate ketones measurably slower than does LDA? Why do bases seemingly as diverse as **11d** (one stereogenic carbon atom and stereogenic nitrogen) and **11c** (two stereogenic carbon atoms and nonstereogenic nitrogen) show comparable stereoselectivity? What is the cause of the observed absolute stereoselection, i.e., why should base **11c** preferentially abstract the axial pro-R hydrogen of compound **6**?



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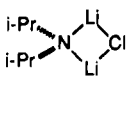

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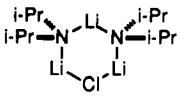

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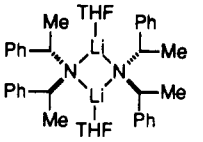
Attempts to analyze the deprotonation of **6** using the highly successful Ireland model[16] did not lead us to answers to any of the above questions. The basic tenet of the Ireland model is that deprotonation with lithium amides is preceded by complexation of the amide to the carbonyl group and involves a pericyclic transition state. It seemed reasonable to explore a possibility that the lithium amide which participates in the transition state is not monomeric but aggregated.[17] Complexation of lithium compounds to one another (aggregation) as well as lithium complexation to electron donors (e.g., the carbonyl group) are current topics of interest.[1i,18] Studies of these phenomena yielded a number of observations which are important in modeling proton abstraction from ketones: (i) Lithium amides and other compounds containing lithium often exist in solution as aggregates. In particular, LDA is present in THF solution mainly as the dimer **15**;[18b] addition of HMPA does not cause this dimer to deaggregate.[18d] (ii) Addition of lithium chloride to a solution of LDA causes the formation of mixed aggregates for which structures **16** and **17** were proposed.[18b] These aggregates exert a strong influence on the stereochemistry of enolization of 2-pentanone.[18b] (iii) A recent ab initio study of metalated aldimines verified a hypothesis that aggregated metalated imines are the reactive species in reactions with electrophiles.[18e,f] A model of interaction of aldimines with aldehydes comprising a mixed LiH–$LiNH_2$ dimer and formaldehyde has been proposed.[18f] (iv) Complexation of lithium to a carbonyl group is often out of plane; that is, the Li atom lies outside the plane defined by the three single bonds originating at the carbonyl carbon.[18g]

Table IV. Relative Energies of Conformers of 19

entry	groups bisecting the ring angle[a] 1	2	3	4	rel energy (kcal/mol)
1	H	Me	H	Me	0
2	H	H	Me	Me	1.5
3	H	Me	H	Ph	2.1
4	H	Me	Me	H	2.5
5	H	Me	H	H	2.8
6	H	Ph	Ph	H	3.5
7	H	Ph	H	Ph	3.7
8	H	Ph	H	H	4.7
9	Me	H	Me	Me	6.3
10	H	H	Me	Ph	7.2
11	H	Me	Ph	H	8.5
12	H	H	H	H	8.6
13	Me	H	Ph	Me	10.0
14	Me	Me	Ph	H	13.6
15	Ph	H	Me	Ph	14.8
16	Ph	H	Ph	Me	17.2
17	H	H	Ph	Ph	17.2
18	Me	Me	Me	Me	19.6
19	Me	Ph	Ph	Me	25.0

[a] Numbers 1–4 correspond to four groups which bisect the ring angles and which are listed clockwise as shown in structure **19a** which represents conformation 1.



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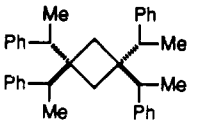
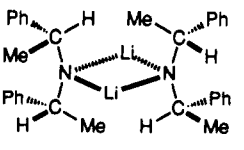
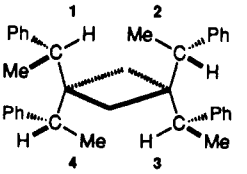


19



18a



19a

In view of the above it seems reasonable to assume that, in THF, chiral lithium amides might exist mainly as dimers analogous to **15**. These dimers could be the reacting species. A dimer of the Li amide **11c** is shown in structure **18**; analysis of interactions between this dimer and the ketone **6** appeared at first hopelessly complicated due to the large number of possible conformers of **18**. Models of all the conformational isomers of the hydrocarbon analogue of **18**, the tetrasubstituted cyclobutane **19**, in which two

(16) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

(17) This possibility has been mentioned before: (a) Moreland, D. W.; Dauben, W. G. *J. Am. Chem. Soc.* **1985**, *107*, 2264. (b) See footnote 27 in ref 16.

(18) Selected recent papers (see ref 18a–c for comprehensive list of references): (a) Du Pue, J.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5518. (b) Galiano-Roth, A. S.; Kim, Y.-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *Ibid.* **1991**, *113*, 5053. (c) Jackman, L. M.; Petrei, M. M.; Smith, B. D. *Ibid.* **1991**, *113*, 3451. (d) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *Ibid.* **1991**, *113*, 5751. (e) Glaser, R.; Streitwieser, A. *J. Org. Chem.* **1991**, *56*, 6612. (f) Glaser, R.; Hadad, C. M.; Wiberg, K. B.; Streitwieser, A. *Ibid.* **1991**, *56*, 6625. (g) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. (h) Olsher, U.; Izatt, R. M.; Bradshaw, J. S.; Dalley, N. K. *Chem. Rev.* **1991**, *91*, 137.

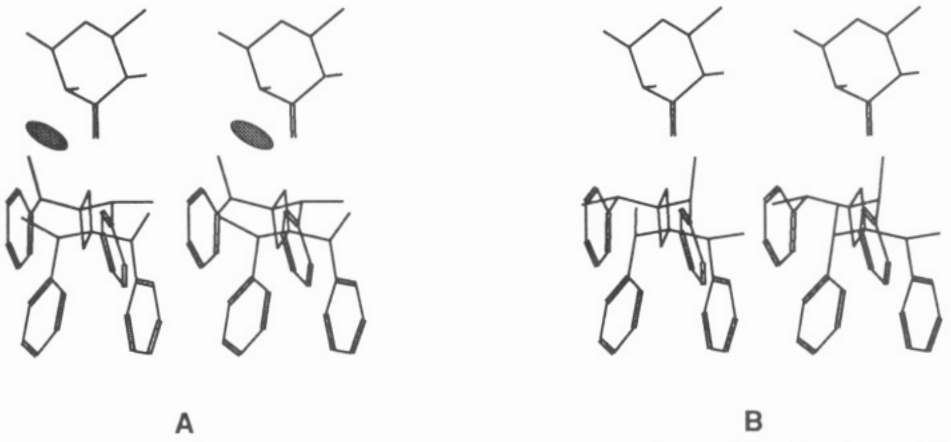
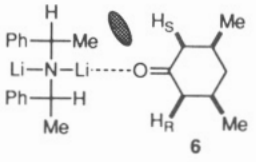


Figure 1. Approach of ketone **6** to the lowest energy conformer of the *R,R* enantiomer of the dimeric base **18a** (stereopair A) and to the *S,S* analogue of **18a** (stereopair B). For clarity, only the two hydrogen atoms which participate in deprotonation are shown.

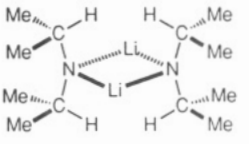
Chart I



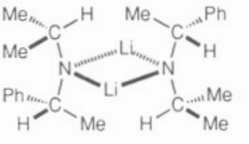
6

of the groups connected to each stereogenic center bisect the appropriate cyclobutane ring angle, were constructed using the molecular modeling software BIOGRAF[19a] and the energies of these isomers were minimized by MM2 method. Nineteen local energy minima were found (Table IV); the conformation lowest in energy had C_2 symmetry and is shown as **19a**. Assuming that the analogous conformer of the amide **18a** is indeed the reactive species we next attempted to visualize the interaction between **18a** and **6**. A pictorial representation of this process has been drawn by analogy with a model of interactions between formaldehyde and a LiH–$LiNH_2$ dimer, proposed by Streitwieser, Wiberg, and Glaser,[18f] and is shown in Figure 1.[20] The ketone, which has replaced one of the THF ligands, interacts with **18a** (stereopair A) and with its enantiomer (stereopair B). Steric hindrance due to the angular methyl group is clearly visible in the stereopair A; the *R,R* base can thus be expected to abstract the pro-R axial proton of **6**. To make the visualization easier the deprotonation of **6** can be represented schematically as shown in Chart I, where a part of the dimer **18a** is drawn as the Fischer projection. It should be noted that the dimer **18a** of the base **11c** is exceptionally easy to analyze; due to the symmetry of this most stable conformer both nitrogen atoms are homotopic, which results in only one Fischer projection being sufficient for this simplified analysis. Also, one of the lithium atoms is clearly hindered by the two phenyl groups and, therefore, it is enough to consider the approach of the ketone from only one side of the projection.

Analogous modeling of the dimers of LDA and the base **11d** led to the conclusion that the most stable dimers of these two bases should correspond to structures **20** and **21**, respectively. In a different system, analysis of interactions of **21** with another cyclic ketone, tropinone, allowed a prediction of the absolute stereochemistry of the product of deprotonation of this ketone with **11d** followed by carboxymethylation.[21]



20



21

In conclusion, a study of enantioselective deprotonation of *cis*-3,5-dimethylcyclohexanone (**6**) with chiral lithium amides, followed by reaction of the nonracemic enolate with electrophiles, revealed that the stereoselectivity of this process depends on the structure of the base used and also on the solvent, the additives, and the nature of the electrophile. The selectivity was modest (up to 79% ee). The reaction of the lithium enolate of **6** with benzaldehyde was stereoselective and yielded only two diastereoisomeric products **8** and **9**. A model has been proposed to explain the enantioselectivity of proton abstraction from cyclic ketones; the model involves a pericyclic transition state which incorporates a lithium amide dimer and the ketone.

Experimental Section

General. All air-sensitive reactions were carried out under argon. Diethyl ether, THF, benzene, and hexane were dried with sodium and distilled under nitrogen from sodium benzophenone ketyl. All amines were distilled under reduced pressure and stored over molecular sieves (4A). Trimethylsilyl chloride was distilled from CaH_2 and stored under argon over Reillex 402 (Aldrich).[22] Lithium bromide was flame dried under argon and then dissolved in THF and used as a 2 M stock solution. Butyllithium was periodically titrated using 2,5-dimethoxybenzyl alcohol as indicator. Amines **10**, **11c**, **11d**, **12c**, and **12d** were synthesized as described in the literature.[13a,23] Ketone **6** was obtained from

(19) (a) Mayo, S. L.; Olafson, B. D.; Goddard, W. A., III. *J. Phys. Chem.* **1990**, *94*, 8897. (b) Since treatment of systems containing main-group metals is difficult because force fields must deal with the oxidation states and the problem of Coulomb attractions vs short-range van der Waals repulsions (this is a topic currently under development; see ref 19a) we have more confidence in calculations of the energies of conformers done on a hydrocarbon (**19**), which should be sufficient to qualitatively visualize the interactions between the reactants. Divalent lithium has not yet been developed in the force field used by us (Dreiding); however, modeling of the amide dimers containing a metal atom (divalent Zn, trivalent B, or tetravalent Sn) produced the same trend as in **19** and the conformer which was the global energy minimum analogous to **18a** in each case.

(20) (a) The approach of the reactants shown in Figure 1 will, ultimately, lead to a transition state involving proton transfer at an acute angle. While, perhaps, counter-intuitive such processes are precedented (Liotta, D.; Saindone, M.; Waykole, L.; Stephens, J.; Grossman, J. *J. Am. Chem. Soc.* **1988**, *110*, 2667) (b) it should be noted that during deprotonation the lithium amide dimer has to either fragment or rearrange to another complex to allow the interaction of the C–H with a tricoordinated nitrogen atom, see refs 18c and 18e for descriptions of similar phenomena in different systems.

(21) Majewski, M., Zheng, G.-Z. Unpublished results.

(22) Hutchinson, D. K. *Aldrichimica Acta* **1986**, *19*, 58.

commercially available 3,5-dimethylcyclohexanol by separating the isomers by column chromatography (PhH:AcOEt = 4:1) followed by Jones oxidation. Flash chromatography[24] was carried out using Merck Kieselgel 60 (230–400 mesh) and TLC was performed on precoated plates (Merck, silica gel 60, F 254). The spots were detected using UV light, iodine, or by dipping a plate in a H_2O solution containing phosphomolybdic acid, $Ce(SO_4)_2$, and H_2SO_4 followed by charring on a hot plate. A methyl silicone gum column (HP-1, 5 m × 0.53 mm) was used in all GC work. Melting and boiling points are uncorrected. All NMR spectra were recorded at 300 (proton) or 75 MHz (carbon) in $CDCl_3$ using tetramethylsilane as internal standard. Molecular mechanics calculations were performed on a Stardent 3010 workstation using the software BIOGRAF.[20a]

General Procedure for Preparation of Chiral Secondary Amines.[25] An aldehyde (20–25 mmol) and $NaBH_3CN$ (10 mmol) were added to the solution of a chiral primary amine (10 mmol) in dry MeOH (40 mL). The solution was cooled in an ice bath, AcOH was added to adjust the pH to 6, and the mixture was stirred overnight at room temperature. Methanol was then removed under reduced pressure, and K_2CO_3 (40 mL of 40% soln) was added. The mixture was extracted with Et_2O (3 × 25 mL), the combined extracts were washed with brine, and the solvent was removed until a total volume of ca. 8 mL remained. The mixture was then cooled (ice bath), acidified with concd HCl, and either extracted with Et_2O (3 × 20 mL) or, in cases where the amine hydrochloride precipitated, the precipitate was collected and washed with Et_2O. The aqueous layer, or the precipitate dissolved in H_2O, was then made basic with 2 M NaOH, and the product was extracted with Et_2O (3 × 25 mL). The combined extracts were washed (brine), dried ($MgSO_4$), and concentrated. The crude amine was purified by distillation.

(*R*)-(+)-*N*-(2′,2′-Dimethylpropyl)-1-phenylethylamine (11a): 55% yield; bp 224 °C; ^{1}H NMR δ 0.87 (s, 9 H), 1.00 (br s, 1 H), 1.29 (d, *J* = 6.5 Hz, 3 H), 2.13 (d, *J* = 11 Hz, 1 H), 2.25 (d, *J* = 11 Hz, 1 H), 3.67 (q, *J* = 6.5 Hz, 1 H), 7.30 (m, 5 H); ^{13}C NMR δ 25.0, 27.7, 31.2, 58.8, 59.9, 126.5, 128.1, 146.4; IR (KBr) 3061, 3025, 2953, 1451 cm^{-1}; MS (CI-NH_3) *m/e* 192 (100, M + 1), 134 (6), 105 (14); $[\alpha]^{22}_D$ +71.8° (*c* = 0.056, $CHCl_3$). Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.68; H, 10.95; N, 7.60.

(*R*)-(+)-*N*-(1′-Ethylpropyl)-1-phenylethylamine (11b): 67% yield; bp 230 °C; ^{1}H NMR δ 0.81 (m, 6 H), 1.32 (d, *J* = 10 Hz, 3 H), 1.35 (m, 5 H), 2.23 (p, *J* = 5.5 Hz, 1 H), 3.84 (q, *J* = 6 Hz, 1 H), 7.25 (m, 5 H); ^{13}C NMR δ 8.8, 9.8, 24.6, 24.9, 26.2, 54.6, 56.0, 126.2, 127.8, 146.1; IR (KBr) 3337, 3061, 3024, 1491 cm^{-1}; MS (CI-NH_3) *m/e* 192 (100, M + 1), 162 (17), 105 (18); $[\alpha]^{22}_D$ +59.6° (*c* = 0.072, $CHCl_3$). Anal. Calcd for $C_{13}N_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.88; H, 11.25; N, 7.55.

(*S*)-(+)-*N*-Benzyl-1-cyclohexylethylamine (12a): 72% yield; bp 101 °C (0.3 mmHg); ^{1}H NMR δ 0.98 (d, *J* = 5 Hz, 3 H), 1.25 (m, 7 H), 1.70 (m, 5 H), 2.47 (m, 1 H), 3.67 (d, *J* = 13 Hz, 1 H), 3.80 (d, *J* = 13 Hz, 1 H), 7.32 (m, 5 H); ^{13}C NMR δ 16.5, 26.3, 26.4, 26.6, 27.8, 29.6, 42.7, 51.3, 56.8, 126.4, 127.8, 128.0, 140.8; IR (KBr) 3326, 3083, 3063 cm^{-1}; MS (CI-NH_3) *m/e* 218 (100, M + 1), 134 (83), 91 (50); $[\alpha]^{22}_D$ +20.8° (*c* = 0.053, $CHCl_3$). Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 83.03; H, 10.81; N, 6.28.

(*S*)-(−)-*N*-Cyclohexyl-1-phenylethylamine (12b): 68% yield; bp 260 °C; ^{1}H NMR δ 1.04 (m, 6 H), 1.27 (d, *J* = 6.5 Hz, 3 H), 1.49 (s, 1 H), 1.64 (m, 3 H), 1.94 (d, *J* = 10 Hz), 1 H), 2.26 (m, 1 H), 3.91 (q, *J* = 6.5 Hz, 1 H), 7.26 (m, 5 H); ^{13}C NMR δ 24.3, 24.5, 25.6, 32.7, 34.0, 52.9, 53.8, 125.8, 126.0, 127.7, 145.8; IR (KBr) 3328, 3059, 3023, 1492 cm^{-1}; MS (CI-NH_3) *m/e* 203 (12, M$^+$), 188 (73), 160 (28), 105 (100), 56 (46); $[\alpha]^{22}_D$ −66.8° (*c* = 0.082, $CHCl_3$). Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.63; H, 10.49; N, 7.00.

General Procedure for the Preparation of the 3,5-Dimethylcyclohexanone Lithium Enolate and Its Reactions with Electrophiles. *n*-Butyllithium (1 equiv, a 1.88 M solution in hexanes) was added dropwise to a 0.2 M solution of an amine (1 equiv) in THF at 0 °C. The mixture was stirred for 1 h at 0 °C and then was cooled to −78 °C and **6** (0.9 equiv 0.5 M solution in THF) was added dropwise over a period of 3 min. The resulting solution was stirred at −78 °C for 2 h and then was treated with Ac_2O (3 equiv) or with PhCHO (0.9 equiv), stirred for 30 min (Ac_2O) or 2 min (PhCHO) and quenched with saturated NH_4Cl solution. The mixture was then allowed to warm to room temperature and was extracted with Et_2O. The combined organic extracts were washed with 0.1 M citric acid and with saturated $NaHCO_3$ solution, and dried ($MgSO_4$), and the solvents were removed.

[2*R-[2α(*S**),3α,5α]]-2-(Hydroxyphenylmethyl)-3,5-dimethylcyclohexanone (8) and [2*S**-[2α(*R**),3β,5β]]-2-(Hydroxyphenylmethyl)-3,5-dimethylcyclohexanone (9).** According to the general procedure the lithium enolate **7** was generated in THF (3 mL) from the amine **12b** (0.112 g, 0.55 mmol), *n*-BuLi (0.55 mmol), and **6** (63 mg, 0.50 mmol, in 1 mL THF). The crude mixture containing the aldols was left overnight under vacuum (0.1 mmHg). The product (71 mg; 61%) contained only compounds **8** and **9** in ratio of 34:66 as measured by NMR and was of sufficient purity for NMR shift reagent analysis: Eu(tfc)$_3$ was added to the NMR sample in portions of ca. 5 mg; sufficient splitting of the C*H*OH signal was observed when the peaks were shifted to δ 6.15 and 5.65 ppm (from the original δ 5.20 and 4.92 ppm), and the ee values were determined to be 51% and 30%, respectively. A pure sample of each compound was obtained by flash chromatography (SiO_2; PhH:AcOEt = 15:1).

Structure Elucidation. The signals in ^{1}H NMR spectra of **8** and **9** were assigned (vide infra) by decoupling experiments and by 2-D Cosy. Compound **8** had J_{ab} of 7.6 Hz and J_{bc} of 5.4 Hz (determined from the ^{1}H NMR spectrum in C_6D_6 after decoupling). Compound **9** had J_{ab} equal to 1.9 Hz and J_{bc} equal to 11.5 Hz. The structures of **8** and **9** were assigned as described in the aldol literature.[10] The theoretical coupling constants obtained by constructing models of all four diastereoisomeric aldols and fitting the relevant dihedral angles into the modified Karplus equation[26] were in agreement with the proposed structures for **8** and **9**.

Compound 8: white solid; mp 106.5–108 °C; R_f 0.16 (15:1 PhH–AcOEt); ^{1}H NMR δ 0.97 (d, *J* = 7 Hz, 3 H, C3-Me), 1.04 (d, *J* = 6 Hz, 3 H, C5-Me), 1.56 (m, 1 H, C4-H), 1.74 (m, 1 H, C4-H), 2.02 (m, 1 H, C3-H), 2.27 (m, 2 H, C5-H and C6-H), 2.46 (dd, *J* = 13, 5 Hz, 1 H, C6-H), 2.46 (dd, *J* = 7.6, 5.4 Hz, 1 H, C2-H), 2.72 (d, *J* = 6 Hz, 1 H, OH), 4.96 (dd, *J* = 7.6, 6 Hz, 1 H, CHO), 7.34 (m, 5 H, arom.-H); ^{13}C NMR δ 19.9, 21.5, 29.8, 31.9, 36.6, 47.5, 63.7, 73.7, 126.3, 127.7, 128.3, 142.7, 213.8; IR (KBr) 3447, 1710 cm^{-1}; MS (EI) *m/e* 232 (4, M$^+$), 214 (14), 126 (38), 111 (100), 107 (40), 105 (29), 84 (32), 79 (39), 77 (46), 69 (30). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.67. Found: C, 77.36; H, 8.46.

Compound 9: white needles (pentane); mp 77–78 °C; R_f 0.23 (15:1 PhH–AcOEt); ^{1}H NMR δ 1.02 (d, *J* = 6 Hz, 3 H, C5-Me), 1.22 (d, *J* = 6, 3 H, C3-Me), 1.30 (m, 1 H, C4-H), 1.95 (m, 2 H, C5-H and C6-H), 2.06 (m, 1 H, C4-H), 2.24 (m, 2 H, C3-H and C6-H), 2.55 (dd, J_1 = 11.5 Hz, J_2 = 1.9 Hz, 1 H, C2-H), 4.08 (d, *J* = 11 Hz, 1 H, OH), 4.92 (dd, *J* = 11, 1.9 Hz, 1 H, CHO), 7.25 (m, 5 H, arom.-H); ^{13}C NMR δ 20.6, 22.2, 34.6, 36.2, 43.5, 51.2, 61.6, 70.8, 125.4, 126.5, 127.9, 143.9, 214.9; IR (KBr) 3509, 1698 cm^{-1}; MS (EI) *m/e* 232 (4, M$^+$), 214 (16), 126 (26), 111 (100), 107 (37), 105 (30), 84 (30), 79 (44), 77 (55), 69 (38). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.67. Found: C, 77.36; H, 8.46.

***cis*-3,5-Dimethyl-1-cyclohexen-1-ol Acetate (13).** According to the general procedure a solution of lithium enolate was produced using **6** (63 mg, 0.50 mmol), *n*-BuLi (0.55 mmol), and **12c** (90 mg, 0.55 mmol) and was acetylated using Ac_2O (0.15 mL, 1.60 mmol). Chromatography (hexane–AcOEt (15:1)) gave the enol acetate **13** as a colorless oil (66.5 mg, 79%): bp 190 °C; ^{1}H NMR δ 0.87 (m, 1 H), 1.00 (m, 6 H), 1.72 (m, 1 H), 1.85 (m, 2 H), 2.03 (m, 1 H), 2.10 (s, 3 H), 2.37 (m, 1 H), 5.20 (s, 1 H); ^{13}C NMR δ 20.7, 21.4, 21.5, 29.2, 30.0, 34.9, 39.9, 119.4, 147.5, 168.9; IR (KBr) 1728 cm^{-1}; MS (CI-NH_3) *m/e* 186 (100, M + NH_4^+), 169 (10, M + 1), 144 (29), 126 (67), 111 (34), 77 (28), 60 (47). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.23; H, 9.47.

(23) Overburger, C. G.; Marullo, M. D.; Durst, H. D. *J. Am. Chem. Soc.* 1971, *93*, 2897.
(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1979, *43*, 2923.
(25) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Org. Chem.* 1961, *83*, 1374.
(26) Haasnoot, C. A.; De Leuw, F. A. A. M.; Altona, C. *Tetrahedron* 1980, *36*, 2783.

The ee of the product was measured by ^1H NMR using Eu(hfc)$_3$ in $CDCl_3$. $[\alpha]^{22}_D$ +9.9° (c = 0.02 M; $CHCl_3$) for a sample having ee of 48% by NMR.

***cis*-[(3,5-Dimethyl-1-cyclohexen-1-yl)oxy]trimethylsilane (14).** *n*-Butyllithium (0.55 mmol, 0.30 mL of a 1.88 M solution in hexanes) was added dropwise to a solution of **12c** (89.9 mg, 0.55 mmol) in THF (3 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then was cooled to −78 °C and TMSCl (0.32 mL; 2.5 mmol) was added followed by dropwise addition of **6** (63 mg; 0.50 mmol) in THF (1 mL). After 1 min Et_3N (1 mL) was added, and the solution was allowed to warm to room temperature. Solvents and excess of the reagents were removed under vacuum and the residue was poured into saturated $NaHCO_3$ solution (10 mL). The product was extracted with Et_2O (2 × 10 mL), and the ether extracts were washed with 0.1 M citric acid (2 × 15 mL) and water. Drying ($MgSO_4$) followed by solvent removal gave the crude product which was purified by flash chromatography (SiO_2, pentane) which yielded **14** (58.5 mg; 59%) as colorless oil: bp 190 °C; ^1H NMR δ 0.18 (s, 9 H), 0.69 (m, 1 H), 0.95 (m, 6 H), 1.66 (m, 3 H), 1.96 (m, 1 H), 2.26 (m, 1 H), 4.70 (s, 1 H); ^{13}C NMR δ 0.3, 22.0, 22.7, 29.7, 30.3, 38.5, 40.8, 110.9, 149.7; IR (neat) 1665 cm^{-1}; MS (CI-NH_3) m/e 199 (100, M + 1), 183 (30), 144 (19), 90 (32). Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18. Found: C, 66.40; H, 11.00.

Acknowledgment. We thank NSERC Canada and the University of Saskatchewan for financial support.

Registry No. **6**, 7214-52-0; **8**, 141396-51-2; **9**, 141396-52-3; **10**, 141396-53-4; **11a**, 122348-66-7; **11b**, 133469-22-4; **11c**, 23294-41-9; **11d**, 87861-38-9; **12a**, 141396-54-5; **12b**, 66399-53-9; **12c**, 19302-32-0; **12d**, 17480-69-2; **13a**, 128350-75-4; **13b**, 141435-15-6; **14a**, 128441-45-2; **14b**, 141435-16-7; PhCHO, 100-52-7; (*R*)-1-phenylethylamine, 3886-69-9; (*S*)-1-cyclohexylethylamine, 17430-98-7; 2,2-dimethylpropanal, 630-19-3; diethyl ketone, 96-22-0; (*S*)-1-phenylethylamine, 2627-86-3; cyclohexanone, 108-94-1.

Diastereoselective Cyclocondensation of Electron-Rich Dienes with Chiral Thio-Substituted Aldehydes

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The Lewis acid-promoted cyclocondensation between two electron-rich dienes with a series of racemic α- and β-thio-substituted aldehydes has been studied. Boron trifluoride etherate proved to be the catalyst of choice, affording satisfactory chemical yields and generally good diastereoselectivities. Other Lewis acidic catalysts gave lower yields and in some cases reversed the sense of the diastereoselection. A rationalization of the stereochemical results is presented.

The Lewis acid (LA)-promoted cyclocondensation of electron-rich dienes with aldehydes recently emerged as a powerful synthetic tool for the stereoselective assembly of a wide range of biologically relevant compounds.[1] Control of the stereochemistry of the reaction[1] has been achieved in three ways: by employing chiral catalysts,[2,3] chiral dienes,[2] and chiral dienophiles.[4-7] Among the latter, alkoxy-[4] and aminoaldehydes[5] were mainly investigated. Chiral thio-substituted aldehydes, however, have not been exploited for this reaction, despite the well-recognized efficiency of sulfur-containing groups as elements of stereocontrol[8] and the impressive number of synthetic

Table I. Diastereoselective Synthesis of Pyranones 9–12, 16, and 17 by Cyclocondensation of Diene 7 with Aldehydes 1–6 in the Presence of LA[a]

aldehyde	LA	product	yield[b] (%)	diastereoisomeric ratio a:b[c]
1	BF_3·OEt_2	**9ab**	54	≥98:2
1	$TiCl_4$	**9ab**	36	≥98:2
1	$TiCl_2$(O-*i*-Pr)$_2$	**9ab**	32	≥98:2
1	VCl_3·THF_3	**9ab**	42	≥98:2
1	$MgBr_2$	**9ab**	37	88:12
1	Eu(fod)$_3$[d]	**9ab**	46	55:45
2	BF_3·OEt_2	**10ab**	56	≥98:2
2	$TiCl_4$	**10ab**	36	51:49
3	BF_3·OEt_2	**11ab**	51	95:5
3	$MgBr_2$	**11ab**	31	59:41
4	BF_3·OEt_2	**12ab**	54	46:54
4	$TiCl_4$	**12ab**	32	≤2:98
5	BF_3·OEt_2	**16ab**	60	40:60
5	$TiCl_4$	**16ab**	33	79:21
6	BF_3·OEt_2	**17ab**	74	54:46
6	$TiCl_4$	**17ab**	30	84:16

[a] Aldehyde:diene:catalyst = 1:1.2:1 mol ratio, at −78 °C unless otherwise stated. [b] Isolated yields. [c] As determined by 300-MHz ^1H NMR spectroscopy. [d] At room temperature.

(1) Reviews: (a) Danishefsky, S. J.; De Ninno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (b) Danishefsky, S. J. *Chemtracts* **1989**, 273.
(2) Bednarsdki, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 7060, and references cited therein.
(3) (a) Quimpere, M.; Jankowski, K. *J. Chem. Soc., Chem. Commun.* **1987**, 676. (b) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.
(4) Recent reports on the use of chiral alkoxy aldehydes: (a) Myles, D. C.; Danishefski, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636. (b) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834.
(5) Recent reports on the use of chiral amino aldehydes: (a) Midland, M. M.; Afonso, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 4368. (b) Jurczak, J.; Golebiowski, A.; Raczko, J. *J. Org. Chem.* **1989**, *54*, 2495. (c) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609. (d) Golebiowski, A.; Raczko, J.; Jacobsson, U.; Jurczak, J. *Tetrahedron* **1991**, *47*, 1053.
(6) For the use of other chiral aldehydes see: (a) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246. (b) Danishefsky, S. J.; Pearson, W. H.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 1280.
(7) For the use of aldehydes bearing a chiral auxiliary see: (a) Bauer, T.; Chapuis, C.; Kozak, J.; Jurczak, J. *Helv. Chim. Acta* **1989**, *72*, 482. (b) Bauer, T.; Kozak, J.; Chapuis, C.; Jurczak, J. *J. Chem. Soc., Chem. Commun.* **1990**, 1178. (c) Bulmann Page, P. C.; Prodger, J. C. *Synlett* **1991**, 84.

0022-3263/92/1957-3605$03.00/0