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A Comparative Study of Solid State and Solution Aldol Addition Reactions of the Lithium Enolate of Methyl 3,3-Dimethylbutanoate: Stereochemistry and Mechanistic Implications

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Abstract: We report the first systematic study of the solid state aldol addition reactions of the lithium enolate of methyl 3,3-dimethylbutanoate with various aliphatic or aromatic, achiral or chiral, solid or liquid aldehydes, in comparison with the same reactions performed in tetrahydrofuran (THF) solution. The diastereoselection of the solid state reactions in all the cases was found to be essentially identical to that of the solution reactions. At low temperatures (< -20 °C), both the solid state and the solution reactions are kinetically selective with the syn:anti ratios of approximately 50:50, except for the reactions involving sterically small aldehydes. Decreasing the bulkiness of the aldehydes from pivalaldehyde to acetaldehyde resulted in changes of the syn:anti ratio from 42:58 to 90:10. At higher temperatures, the stereoselection of both the solid state and the solution reactions is thermodynamically controlled, giving predominately anti isomers. The solid state reactions generally afforded low yields and low conversions of the aldehydes. Increasing the reaction time or temperature had little effect on the yields of the solid state reactions. The stereochemical outcomes can be interpreted satisfactorily using the Zimmerman-Traxler-Dubois transition state models. The results suggest that the same reacting species and transition states are involved in both the solid state and the solution reactions under our experimental conditions.

INTRODUCTION

The chemistry of lithium enolates has attracted the interest of many chemists of all disciplines because of the great synthetic value of these compounds. Many studies are directed at elucidating the relations of the structure of the lithium enolates to the reactivity and stereochemistry in the reactions of the enolates with electrophiles.[1-3] It is well established that organolithium compounds such as lithium enolates exist as aggregated contact ion pairs (e.g. dimers, tetramers, hexamers, etc.) in both solid state and nonpolar or weakly polar solvents.[1] The degree of aggregation strongly depends on solvent and added complexing or chelating agents and is often independent of particular enolate structure.[1,4-7] Formation of dimers tend to be favored in the presence of ethylenediamine, tetramers in solvents such as THF, and hexamers in non-donor hydrocarbon solvents. There is a growing body of evidence indicating that organolithium aggregates in solutions can function as the primary reactants in reactions with electrophiles[8-10] and therefore the degree of aggregation may influence the rate, regiochemistry, and stereochemistry of the reactions. For examples, using a rapid-injection NMR technique, McGarrity and his coworkers demonstrated that butyllithium in both dimeric and tetrameric forms can directly react with benzaldehyde in THF at -85 °C but the reaction rate of the dimer is about 10 times higher than that of the tetramer.[8] Recently, Jackman's group[11] reported some very interesting results on transesterification of lithium 3,5-dimethylphenolate aggregates with a series of 3,5-dimethylphenyl esters in weakly polar, aprotic solvents. They found that the tetramer reacts ~20 and ~3-4 times slower than the dimer and the hexamer, respectively, under the same conditions.[11] The addition of lithium salts, or production of lithium salts during the reactions of lithium enolate aggregates in solution with electrophiles, may lead to formation of mixed aggregates, which

could alter the nature of primary reactants and the structure of the transition states.[9,12,13]

Although many studies indicate that regio- and stereochemistry of the reactions of lithium enolates with electrophiles depends on the degree of aggregation of the enolates, there is still lack of an unequivocal answer to a key question, i. e. what are the structures of these enolates that actually react in solution? For example, the mixed amide and enolate aggregates were demonstrated[10] to play an important role in the enantioselectivities of aldol reactions and Michael additions of lithium enolates in the presence of an optically active lithium amide. However, it remains unclear whether a dimer or a tetramer is the reactive species. The regiochemistry in alkylation of some lithium enolates was implicated to be controlled by aggregates and mixed aggregates[9,14], but the actual reacting species was not identified. Davis and his coworkers[15] suggested that aggregation might also affect the asymmetric oxidation of enolates by enantiomerically pure (camphorylsulfonyl)oxaziridines, particularly when hexamethylphosphoramide (HMPA) was added to the reactions. Although in the subsequent theoretical studies it was proposed[16] that the transition states involves a monomeric enolate, the identities of the reacting species in these oxidation reactions have not been established experimentally. Recently, we attempted to answer this question via a different approach, i.e. the solid state reactions of enolates.[17] Because of the pioneering work by Seebach[18], Jackman[19], Arnett[20], Williard[21] and others[22], the structures of many enolates in the solid state as single crystals and in solution have been elucidated and a strong similarity between the crystal structures of the enolates and their aggregation state in solution has been established. We reasoned that if a solid enolate of known crystal structure (therefore, known degree of aggregation) was allowed to react heterogeneously with an electrophile in the solid state, the reacting species could be largely limited to the enolate of that specific structure. By comparison of the stereochemical outcome of the reactions in the solid state with that in solution, we might be able to identify the actual reacting species involved in both the solid state and solution reactions. Towards this goal, we have carried out a series of studies.

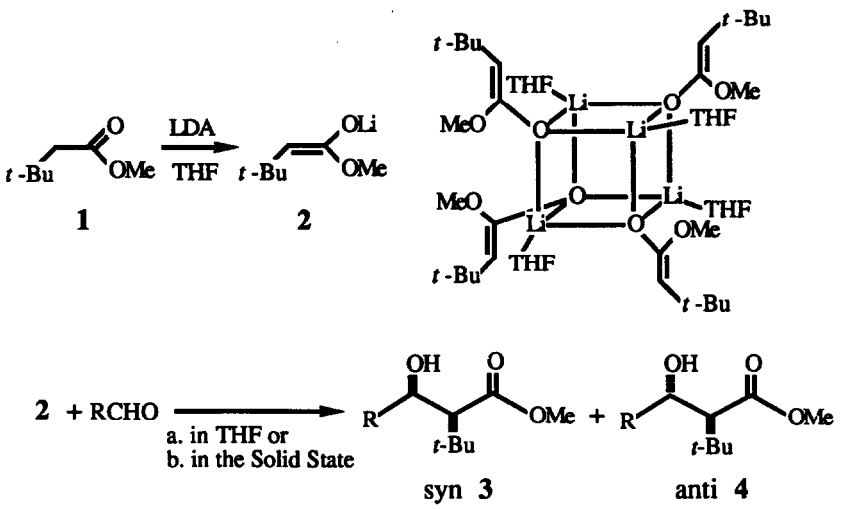
In this paper, we report the results of the first systematic investigation on the aldol addition reactions of a lithium enolate **2** derived from methyl 3,3- dimethylbutanoate (**1**) with a variety of aldehydes in both the solid state and solution (Scheme 1) to yield syn (**3**) and/or anti (**4**) diastereomeric aldols. The lithium enolate **2** of methyl 3,3- dimethyl butanoate was selected because it is one of very few enolates that is stable at room temperature and its X-ray crystallographic structure has been well established by Seebach and his coworkers[5] We choose the aldol addition reaction as the first system to study in detail because of the great importance of the classical base-catalyzed aldol addition reactions in synthetic organic chemistry.[2,3,23,24] Furthermore, no systematic study of the aldol addition reactions of **2** *either in solution or in the solid state* has been reported in the literature. The effects of the reaction parameters, such as the structure of the aldehydes, temperature and time, on the yield and diastereoselectivity of the aldol reactions in the solid state and in solution are discussed and interpreted with consideration of the involvement of the aggregates in the reactions. We have also attempted to identify the reacting enolate species in these aldol reactions.

RESULTS

The lithium ester enolate (**2**) was prepared as a white solid by treating methyl 3,3-dimethylbutanoate (**1**) with freshly made LDA in THF at -78° C[5,25]. Ireland and coworkers[25] reported that the *E* enolate[26] formed predominantly under such reaction conditions, which was supported by NMR analysis of the product from trapping **2** with *t* -butyldimethylsilyl chloride. The X-ray crystallographic study[5] showed that the enolate **2** exists as a tetrameric aggregate having a Li_4O_4 cubic structure as illustrated in Scheme 1. Four lithium and four oxygen atoms of the enolate tetramer occupy alternatively the eight corners of the cube and each lithium atom is surrounded by three enolate oxygens and one THF oxygen. Seebach's group[5] found that the enolate **2** in the solid state could be handled without serious problem at room temperature. This has been confirmed in our laboratory. The yield and stereochemical outcome were approximately the same for the aldol reactions whether the enolate **2** was freshly prepared or had been isolated and stored in solid form for about 3 days with exclusion of air and moisture at room temperature. The solid lithium enolate **2** undergoes aldol addition reactions in both the solid state and solution with aromatic, aliphatic, and chiral aldehydes under various reaction conditions. The

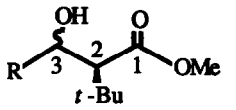
results are described in the following sections.

Scheme 1



Solid state and solution aldol reactions of lithium enolate 2 with solid aromatic aldehydes at -78 °C. Fine powder of the enolate **2** was treated with various aromatic and heteroaromatic aldehydes, which are also solid and were ground into fine powder prior mixing with **2**, under an argon atmosphere at -78 °C for 4 hours. At the end of the 4 hours, the reaction mixture remained solid. The reaction was then quenched with saturated aqueous NH_4Cl solution followed by extraction of the product with ether. The crude product was obtained after evaporation of ether and was further purified by preparative TLC. The characterization of the product using ^{1}H-NMR spectroscopy revealed the formation of syn and anti aldols, **3** and **4**, respectively. Since the signal of the proton attached to C(2) for the syn aldol **3** (e.g. δ = 2.85 ppm when R is *o*-$CH_3OC_6H_4$-) is well separated from that for the anti aldol **4** (δ = 2.60 ppm), the ratio of the diastereomers can be readily determined from the ^{1}H-NMR spectroscopy based on the integrations of the HC(2) signals (Table I). Both HC(2) signals appear as doublets resulted from the vicinal coupling between the protons on C(2) and C(3). It is known[2] that the vicinal coupling constant for a syn aldol isomer (2-6 Hz) is usually less than that for the anti isomer (7-10 Hz). The substantial difference in the coupling constants (J in Hz as shown in Table I) allows an unambiguous assignment for the syn and anti diastereomers. For comparison, the aldol reactions were also run in THF at -78 °C for 4 hours. The aldol products were characterized in the same manner as it was described for the solid state reaction. It should be noted that there are few reports in the literature on the solution aldol addition reactions of the lithium ester enolate **2**. As shown in Table I, the ratios of the diastereomers **3** and **4** obtained in solution and solid state were found to be practically identical. In general, the syn:anti ratio was approximately 50:50 regardless of the nature and position of the substituents on the phenyl ring. The ratios of the aldol diastereomers were further confirmed by gas-liquid chromatography (GLC). To ensure that the syn:anti ratios were not affected by the purification process, the crude aldol products were also analyzed by NMR and GLC and the ratios of diastereomers were the same as those obtained for the purified aldols. The only appreciable difference between the solution and the solid state reactions is the yields. For the solution reactions, the isolated yield ranges from reputable to almost quantitative (i.e. 58 to 98%). In contrast, the solid state reactions give much lower yields in the range of 10 to 30%. The low yields for these solid state aldol reactions should be expected because many other types of solid state reactions, such as pinacol rearrangement, Baeyer-Villiger oxidation, Wittig-Horner reaction, etc., have been reported to afford low yields.[27]

Table I. Aldol Products from Addition of the Lithium Ester Enolate 2 to Aldehydes (RCHO) in the Solid State and in THF Solution at -78°C.

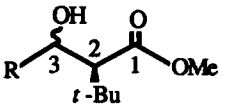


entry	RCHO		J HC(2) in Hz		syn:anti		yield (%)	
	R =	m.p.(°C)	syn	anti	THF[a]	Solid[b]	THF[a]	Solid[b]
1	2-$CH_3OC_6H_4$-	39	10.1	3.3	56:44	53:47	94	29
2	4-ClC_6H_4-	50	10.0	3.4	51:49	44:56	73	31
3	4-$NO_2C_6H_4$-	108	9.5	2.9	44:56	53:47	96	18
4	3-$NO_2C_6H_4$-	59	9.8	2.4	56:44	59:41	98	12
5	2-$NO_2C_6H_4$-	46	10.1	1.8	45:55	46:54	97	17
6	5-NO_2-2-furyl	39	9.3	2.9	41:59	44: 56	58	10
7	5-NO_2-2-thienyl	77	9.6	2.3	39:61	46:54	66	19

a. Reactions run in THF solution for 4 h. b. Reactions run in the solid state for 4 h.

Solid state and solution aldol reaction of lithium enolate 2 with solid aldehydes at 22°C. Taking advantage of the stability of the enolate 2 at higher temperatures, the above aldol addition reactions were also carried out at 22 °C in both the solid state and THF solution and the results are summarized in Table II. The yields for the solution reactions are reputable (54-75%) but lower than those obtained at -78 °C, which could be attributed to the side reactions favored at higher temperatures. For the solid state reactions, the yields remain lower than those for the solution reactions but comparable to those for the solid state reactions at -78 °C in most cases. The aldol addition of 2 to *o*-anisaldehyde in the solid state gave an exceptionally high yield of 70% (Table II, entry 1). The reason for this is not yet clear and further investigation is in progress in our laboratory. In contrast to the reactions at -78 °C, a high diastereoselectivity was observed for the reactions at 22 °C in both the solid state and solution with the anti aldol 4 being the predominant product. However, the syn:anti ratios for the solid state reactions were found, again, to be very similar to those for the solution reactions. The high selectivity in favor of the anti aldol 4 at 22 °C could be resulted from the thermodynamically controlled syn-anti equilibration of the aldolates.[2] To test this possibility, the aldol reactions of 2 were performed at -78 °C and were allowed to warm up to then maintained for a period of time at room temperature before quenching. The aldols such obtained were found to have high content of the anti isomer. For example, the reaction of 2 with *p*-chlorobenzaldehyde performed at -78 °C in THF for 4 hours afforded the aldols with syn-anti ratios of 51:49 when quenched at -78 °C and of 2:98 when quenched after warming up and maintaining at 22 °C for 15 h. These results indicate that the syn-anti equilibration is mainly responsible for the observed high anti selectivity at 22 °C. Mulzer and coworkers[28] reported that the diastereoselection was thermodynamically controlled in the aldol reactions of carboxylic acid dianions with aldehydes in solution at high temperatures (e.g. 22 °C) and long reaction times (e.g. 48 h). To examine whether the aldol reactions of 2 are thermodynamically or kinetically controlled under various conditions, the effect of reaction temperature and time on the diastereoselectivity was investigated systematically.

Table II. Aldol Products from Addition of the Lithium Ester Enolate 2 to Aldehydes (RCHO) in the Solid State and in THF Solution at 22 °C.



Entry	RCHO, R =	syn:anti		yield (%)	
		THF[a]	Solid[b]	THF[a]	Solid[b]
1	2-$CH_3OC_6H_4$-	~0:100	8:92	75	70
2	4-ClC_6H_4-	1:99	9:91	60	22
3	4-$NO_2C_6H_4$-	20:80	2:98	54	22
4	3-$NO_2C_6H_4$-	12:88	~0:100	57	16
5	2-$NO_2C_6H_4$-	3:97	~0:100	71	23
6	5-NO_2-2-thienyl	c	~0:100	c	29

a. Reactions run in THF solution for 4 hours; b. Reactions run in the solid state for 3 days; c. Not a clean reaction.

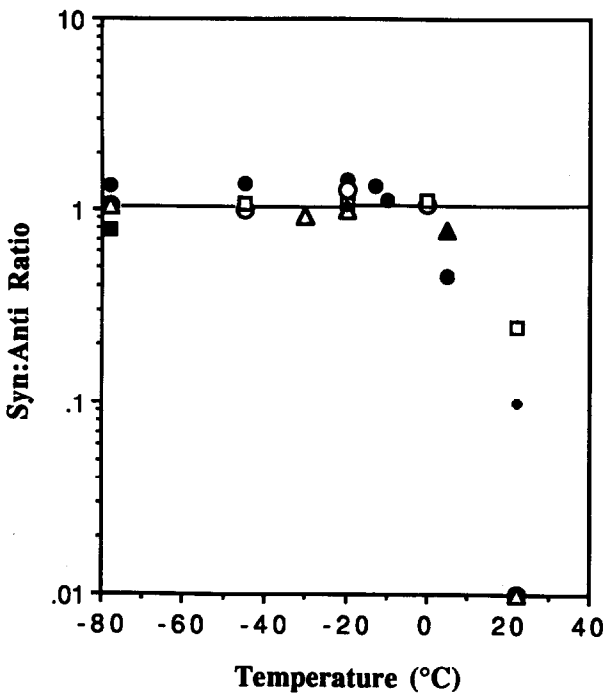


Figure 1. Effect of reaction temperature on syn:anti ratio of the aldol products obtained from the additions of the lithium enolate **2** to (●) *o*-anisaldehyde, (O) *p*-chlorobenzaldehyde and (□) *p*-nitrobenzaldehyde in THF for 4 h, and to (Δ) benzaldehyde and (♦) *p*-chlorobenzaldehyde in the solid state for 4 h.

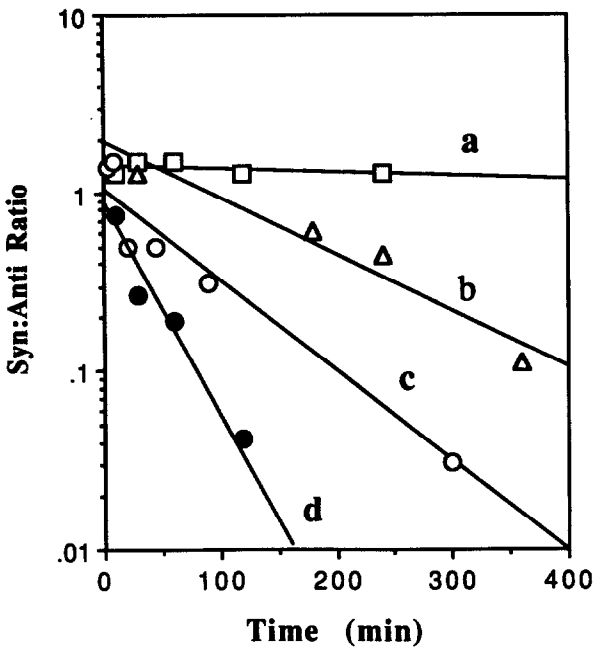


Figure 2. Effect of reaction time on syn:anti ratio of the aldol products obtained from the additions of the lithium enolate **2** to *o*-anisaldehyde at (a) -78 °C, (b) 0 °C and (d) 22 °C, and to (c) *o*-nitrobenzaldehyde at 22 °C in THF.

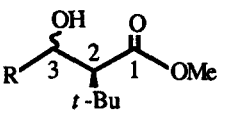
Effect of reaction temperature and time on diastereoselectivity. Aldol reactions of **2** with aromatic aldehydes were carried out at various temperatures in the range of -78 to 22 °C in both the solid state and THF solution for 4 h. The relationship between the syn:anti ratio of the aldol products and the reaction temperature is demonstrated in Figure 1. For all reactions, the syn:anti ratios remain practically the same (~50:50) up to temperatures about -20 to 0 °C. Above 0°C, the ratios change dramatically in favor of the anti products to < 10:90. Thus, the stereoselection of both the solid state and solution reactions is independent of reaction temperature at lower temperatures (e.g.-78 °C to ~-20 °C) while it is strongly temperature dependent at higher temperatures (e.g. ~-20 °C to 22 °C). The yields of the solution reactions tend to decrease when the temperature is raised. It is noteworthy that the temperature has little effect on the yields of the solid state reactions. For example, the addition of **2** to *p*-chlorobenzaldehyde in the solid state had yields of 31, 29, 28 and 22% at temperatures of -78, -20, 5 and 22 °C, respectively.

To examine the effect of reaction time, the aldol reactions in THF were performed and quenched at a constant temperature at various time intervals. As shown in Figure 2, the ratios of the syn:anti aldols are largely independent of reaction time at low temperatures (e.g. -78 °C, Figure 2a) but decrease significantly with time at higher temperatures (e.g. 0 and 22 °C, Figures 2b, 2c and 2d). The rate of conversion of syn isomers into anti isomers increases greatly with increase in the reaction temperature. For example, the reaction of **2** with *o*-anisaldehyde quenched after 30 min at 0 °C (Figure 2b) afforded the aldols with a syn:anti ratio of 56:44 and the reaction quenched after 180 min gave a syn:anti ratio of 32:68. However, the same reactions at 22 °C (Figure 2d) resulted in the syn:anti ratios of 21:79 and 4:96 after 30 and 120 min, respectively. These results indicate that the initially formed kinetic aldolates are converted into more stable thermodynamic anti aldolates at higher temperatures and that such a conversion is not significant at lower temperatures. Therefore, the syn:anti ratios

obtained at low temperatures (e.g. -78 °C) and at very short reaction times should represent the kinetic selectivity of the reactions. Furthermore, an increase in anti isomer content was observed when an aldol product of known syn:anti composition (e.g. 51:49, entry 2 in Table I) was treated under the reaction conditions at 22 °C for 4 h. In the solution reactions, the reaction time (longer than 10 min) has little effect on the yields. Similarly, the yields of the solid state reactions remained low and practically unchanged at reaction times longer than 4 h. For examples, the *o*-anisaldehyde reactions in THF at -78 °C gave yields of 87% at 10 min, 95% at 30 min and 94% at 240 min and the *p*-chlorobenzaldehyde reactions in the solid state at 22 °C had yields of 20% at 4 h, 24% at 24 h, 22% at 72 h and 17% at ~1 week.

Solid state and solution aldol reaction of lithium enolate 2 with liquid aldehydes at -78 °C. Intrigued by the results from the reactions of the solid lithium enolate 2 with solid aldehydes, we carried out the solid state aldol addition of the solid lithium enolate 2 to the aldehydes, which are liquid at room temperature. Thus, the liquid aldehyde such as acetaldehyde was added dropwise to the solid lithium enolate, which was kept at -78 °C with stirring. For the aldehydes having melting points higher than -78°C (Table III), the mixing was quite thorough as well because the liquid drops were soaked in the dry solid enolate before freezing. Upon completing addition of the aldehyde, the reaction mixture remained solid and the aldol products were isolated after 4 h at -78 °C. For comparison, the same reactions were performed in THF at -78 °C. Again, we have found that the syn:anti ratios of the diastereomers isolated from the solid-liquid reactions were very similar to those from the corresponding THF solution reactions as shown in Table III. In general, the yields of the solid-liquid reactions were lower than those of the solution reactions but seem to be slightly higher than those of the solid-solid reactions (see Tables I and II and compare with Table III). The size of the R group in the aldehydes appeared to have a significant effect on the stereoselectivity of the reactions. The bulkier the R group in the aldehydes, the greater the content of anti isomers (i.e. the less diastereoselectivity of the reactions). In the case of acetaldehyde (R = CH_3, Table III) the ratio of syn:anti isomers was 90:10. However, when the R was *t*-butyl group, the syn:anti ratio changed drastically to 42:58.

Table III. Aldol Products from Addition of the Lithium Ester Enolate 2 to Aldehydes (RCHO) in the Solid State and in THF Solution at -78 °C.



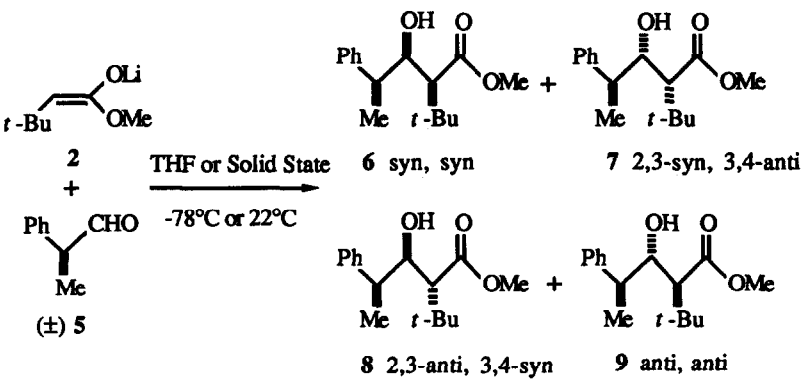
entry	RCHO		HC(2) in Hz		syn:anti		yield (%)	
	R =	m.p.(°C)	syn	anti	THF[a]	Solid[b]	THF[a]	Solid[b]
1	CH_3-	-125	8.5	-	90:10	81:19	92	29
2	C_2H_5-	-81	8.8	2.1	76:24	78:22	90	39
3	*n*-C_3H_7-	-96	8.6	-	70:30	68:32	85	30
4	*i*-C_3H_7-	-65	10.3	1.8	69:31	69:31	88	35
5	*t*-C_4H_9-	6	-	2.2	42:58	41:59	81	23
6	C_6H_5-	-26	9.9	3.8	61:39[c]	51:49	93	31
7	2-furyl	-36	10.0	4.9	62:38	59:41	95	18

a. Reactions run in THF solution for 4 h. b. Reactions run in the solid state for 4 h. c. This value agrees well with that in the literature.[44]

Diastereofacial selectivity in the aldol reaction of the lithium enolate 2 with chiral aldehydes in THF and the solid state. Reaction of an achiral enolate with a chiral aldehyde also gives rise to a mixture of diastereomers. A number of aldol addition reactions involving chiral aldehydes have been reported.[29,30] Diastereofacial selectivity in these reactions is usually rationalized by invoking either the Felkin-

Anh or the Cram chelated transition-state models.[2,3,31] We studied the reactions of lithium enolate **2** with two chiral aldehydes, (±)-2-phenyl propanal **5** and D-(+)-2,3-isopropylidine glyceraldehyde[32] both in THF and in the solid state. For the reactions of **2** with (±)-2-phenyl propanal **5**, there are four possible aldol diastereomers **6**-**9** as depicted in Scheme 2.

Scheme 2



In THF at -78 °C, the reaction between **2** and **5** gave a good yield of 70%. The 3,4-syn:anti selectivity of 44:56 (i.e. the ratio of the isomers **6** plus **8** to the isomers **7** plus **9**) was based on the integration of methyl protons attached to C(4) carbon from ^{1}H-NMR spectroscopy. Gas-liquid chromatography of the aldol products showed 3 peaks at retention times of 9.1, 9.6 and 10.6 min with the peak area ratio of 56:2:42. In the solid state, the reaction at -78 °C gave a mixture of aldols in a yield of 12%. The stereochemical outcomes were the same as those in the solution reaction. The syn:anti ratio as determined by NMR was 51:49 and the GLC exhibited 3 peaks with the area ratio of 42:4:54. When the reactions were performed at 22 °C both in the solid state and in THF, the GLC of the products shows that the peak with retention time of 9.1 min is predominant and accounts for >95% of the total peak areas. Only a trace of the peak at 10.6 min remained. Assuming that thermodynamic selection would also favor the 2,3-anti isomers in this case, the peak at 9.1 min could be assigned to the diastereomer **8** or **9** or both. The 3,4-syn:anti ratio was found to be ~0:100 based on ^{1}H NMR measurement. Therefore, the peak at 9.1 min most likely corresponds to the diastereomer **9**, which should be thermodynamically most favorable because of its anti-anti structure.

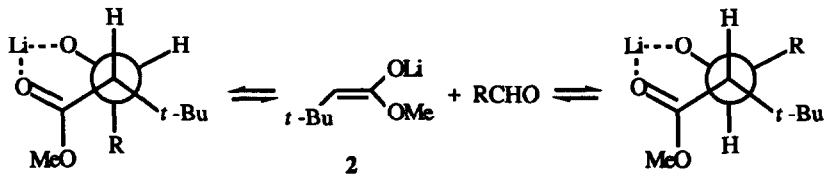
The aldol reactions of **2** with an optically active D-(+)-2,3-isopropylidine glyceraldehyde[32] ($[\alpha]_D$: +70° at 20 °C in chloroform) was also carried out both in the solid state and in THF solution at -78 °C. In these reactions, all of the 4 expected diastereomers were detected in the aldol products. The GLC of the solution reaction product showed 4 peaks at retention times of 8.4, 8.8, 8.9 and 9.3 min with the peak area ratio of 44: 5:5:46. For the solid state reaction, the ratio of the 4 diastereomers was 46:9:4:41. The mixture of the aldol products was found to be optically active with $[\alpha]_D$ of -2.9° and -3.9° measured at 20 °C in chloroform for the products from the solution and the solid state reactions, respectively. These results have again demonstrated that the stereochemical outcomes of the solid state aldol reactions are approximately the same as those of the solution reactions.

DISCUSSION

It has been well documented[2] that the aldolates produced in an addition reaction can undergo syn-anti equilibration by either enolization or reverse aldolation and that the selectivity of the reaction could be under

either thermodynamic or kinetic control. If the aldol reaction is performed under conditions of thermodynamic control, the anti isomer generally predominates over the syn isomer because of the favorable conformation of the anti aldolate. Our results are consistent with that the stereoselection of aldol addition of **2** to aldehydes (RCHO) both in the solid state and in solution is thermodynamically controlled in favor of the anti products at higher temperatures (e.g. > -20 °C, Figure 1). This is understandable by consideration of the Newman projections of the chelated aldolates.[2] As depicted in Scheme 3, the conformation for the anti aldolate have fewer gauche interactions and should be more favored over that for the syn aldolate. In contrast, at lower temperatures (particularly at -78 °C, Figure 2a), the stereoselection of the reactions is mainly kinetically controlled. We do not yet understand why there is a turning point in the mode of stereoselection at about -20 °C as shown in Figure 1 and further studies are in progress in our laboratory. However, all the results clearly indicate that the stereochemical outcomes from both the solid state and the solution reactions at -78 °C represent the kinetic selectivities of the reactions and can be used in discussion of the reaction mechanism.

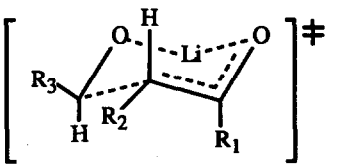
Scheme 3



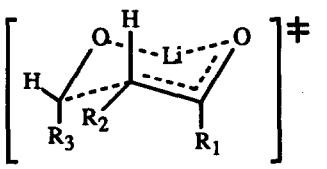
10 Syn aldolate **2** **11** Anti aldolate

There are several types of proposed transition state models in the literature in an effort to explain kinetic stereoselection in aldol addition reactions conducted in solution.[2] In most of these models the state of the enolate aggregation was not taken into account. For example, the closed chair transition states as shown in Scheme 4 for *E* enolates (**12** and **13**), proposed by Zimmerman and Traxler,[33] suffice to explain the observed general trends that *E* and *Z* enolates tend to give anti and syn aldols, respectively.

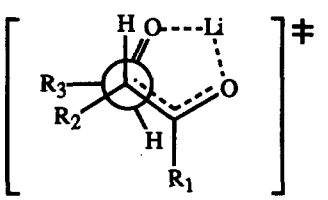
Scheme 4



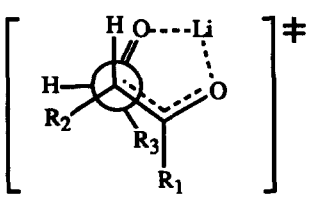
12 *E* to anti



13 *E* to syn



14 *E* to anti



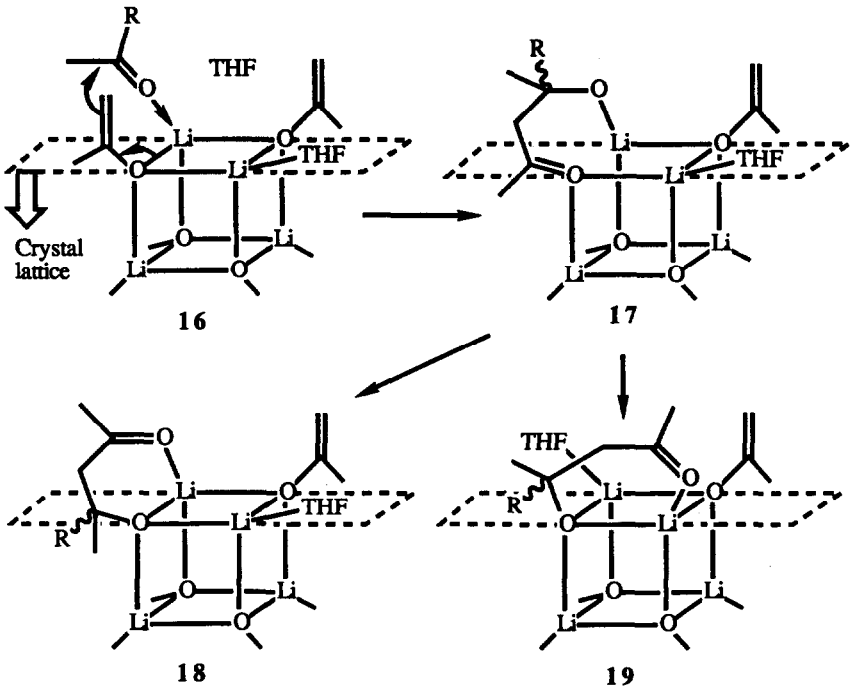
15 *E* to syn

However, the idealized Zimmerman-Traxler transition states could not account for the observations that *E* enolates often lack stereoselectivity or are much less stereoselective than *Z* enolates when R_1 is not large[34] and that bulkiness of the R_2 group has pronounced effect on the stereoselectivity of the aldol reactions.[35,36] A modified model was proposed[34,36] with a skewing of the transition states from the idealized staggered arrangements (Scheme 4, **14** and **15** for *E* enolate). According to this Zimmerman-Traxler-Dubois model, for *E* enolates the importance of steric interaction between R_2 and R_3 (**14**) could be comparable to that between R_1 and R_3 (**15**) unless R_1 is very large, resulting in less diastereoselectivity. When both R_2 and R_3 groups are larger, the difference in the importance between transition states **14** and **15** should become even smaller leading to lesser or lack of stereoselection in the reactions of *E* enolates. Thus, the general lack of kinetic stereoselection (i.e syn:anti ~ 50:50) in the aldol addition of the *E* lithium enolate **2** to the aromatic aldehydes both in the solid state and in solution at -78 °C (e.g. Table I) could be readily interpreted based on this skewed transition state model because the *t*-butyl (R_2), aromatic (R_3) and methoxy (R_1) groups could be rated as very large, large and relatively small, respectively. Likewise, this model could also explain the stereochemical outcomes of the reactions of the *E*- **2** with the aliphatic aldehydes of various bulkiness (Table III). Since the *t*-butyl group (R_2) is very large, a relatively small methyl group as R_3 would favor the transition state **15** rather than **14**, leading to the observed high syn:anti ratio (90:10). As the bulk of R_2 increases from methyl up to *t*-butyl, the importance of the R_1-R_3 interaction should become greater than that of R_2-R_3, leading to the gradual decrease in the observed syn:anti ratios down to 48:52. Another interesting model proposed by Evans and coworkers[3], which considers both chair and boat arrangements in the closed transition states, could also account for the observed stereochemical outcomes as well as the skewed model.[17]

The above models appear to explain the aldol reactions of **2** with aldehydes satisfactorily without considering the aggregate structure. It has been suggested[2] that even if a lithium enolate reacts as a tetramer, a closed transition state in solution reactions is still possible. There are several propositions on mechanisms of reactions with consideration of the structures of enolate aggregates in solution.[11,21c,30e,37] One of the common themes of these proposals is that the reactions of an enolate aggregate begin with substitution of one of complexing solvent molecules in the aggregate by an electrophile and end with the final product still in an aggregate state. For example, Seebach and coworkers[37] postulated a general mechanism for aldol addition reaction of tetrameric aggregate of lithium enolate with ketone or aldehyde in solution, in which the Li_4O_4 cube of the aggregate remains intact throughout entire reaction. This scheme can be used similarly for the solid state aldol addition as depicted in Scheme 5, assuming that the reactions occur on the surface of the enolate cubic crystals. The first step could involve substitution of one of the two THF molecules that are on the surface of the solid enolate **16** by a carbonyl substrate. The aldol reaction would than take place between the substrate and one of two adjacent enolate moieties leading to the aldolate **17**. The temporary opening in the Li_4O_4 cube could be filled by switching positions of two oxygen atoms in the aldolate to give **18** or by replacing the carbonyl oxygen with the aldolate oxygen followed by switching position of THF to give **19**. During the entire process, the aldolate product is always bonded to surface of the solid. In the solid state aldol reactions of **2**, one of the two THF molecules on the surface of the crystal could be replaced by incoming aldehyde in the first step in Scheme 5, while in the solution aldol reactions of **2** any one of the four THF molecules could be replaced. In both cases, the Zimmerman-Traxler-Dubois closed transition states are possible and lead to the same stereochemical outcomes. However, this may not necessarily mean that the state of aggregation and the nature of ligands in the aggregate play no role in the transition states in this case. Recently, Arnett and coworkers[38] discovered that in THF solvent the tetrameric enolate is converted to the tetrameric aldolate but in other solvents the dimeric and hexameric enolate aggregates are also converted to the tetrameric aldolates. They cautioned that the Seebach's mechanism might not be a general one, especially in non-ether solvents.[38] We have some evidence suggesting that changes in the structures of aggregates caused by added lithium salts could influence the stereoselection of the solution aldol reactions of **2** to certain extent. For example, the reaction of **2** with *p*-chlorobenzaldehyde at -78 °C in 1,3-dioxolane led to the aldol products with syn:anti ratio of 55:45. However, the same reactions of **2** in the presence of 1 and 2 equivalents of $LiClO_4$ gave syn:anti ratios of 36:64 and 27:73, respectively. Further

increase in the amount of $LiClO_4$ to 3 equivalents resulted in little change in the syn:anti ratio (~27:73). It is well known that organolithium compounds often form mixed aggregates in the presence of added lithium salts.[9,12,13] Although it is not certain whether the mixed species still maintain the parent degree of aggregation in some cases, there is little doubt that the reactivity,[11] regiochemistry,[9] and stereochemistry[39] of the reactions of the mixed aggregates could be significantly different from the parent homoaggregates.

Scheme 5



Since the existence of enolate aggregates in solution has been established unambiguously, many researchers have been exploring whether the aggregates can function as primary reactants in the reactions or they are merely the pre-equilibrium precursors of monomeric reactants.[1] The thermodynamic parameters,[38] rates,[8,11] and regioselectivities[9] of the reactions in solution were found to be dependent of the degree of aggregation. For example, a careful study has been reported by Arnett and coworkers[38] on the thermochemical analysis of the aldol reaction of lithiopinacolonate with pivalaldehyde in nonpolar media. They found that the enthalpy of reaction of the hexameric enolate was about 5-6 and 2 kcal/mol more exothermic than for the tetrameric enolate and for the dimeric enolate, respectively. These results suggest that the aggregates at various degrees of aggregation can react directly and independently in solution reactions. One of our important findings in this work is that the solid state aldol addition reactions of the lithium enolate **2** with various aldehydes - aliphatic or aromatic and chiral or achiral - have essentially identical kinetic selectivity as the same reactions performed in solution. This strongly suggests that the same reacting species and transition states are involved in both the solid state and the solution reactions under our experimental conditions.

Additional Comments and Observations. In solution reactions, a tetrameric enolate aggregate could dissociate into and equilibrate with dimeric and monomeric enolates. However, it is unlikely for the same dissociation and equilibration to occur in the solid state reactions because of lack of solvation. Thus, the enolate aggregate **2** could be the actual reacting species and function as the primary reactant in the solid state aldol

addition reactions *if the reactions were truly heterogeneous*. The solid state organic reactions between solid and gas, liquid or solid reactants often give higher regio- and stereoselectivities than their corresponding solution reactions.[14,27,40,41] The detailed courses of the solid state reactions are frequently interpretable in terms of conformation and/or packing of the reactant molecules. However, to identify the actual reacting species in the aldol reactions under our experimental conditions, one must substantiate whether the reaction is truly heterogeneous solid state (i.e. the aldehyde molecules directly attack on the ordered lattice of the crystalline enolate) or is merely a homogeneous reaction in melt or in solution without added solvent (i.e. one or more of the species such as reactants in the mixture function as solvent). In the latter case, the reaction occurs in a fluid state in the interfacial region and the reacting species can not be identified definitively.

There are several experimental observations that seem to support the heterogeneous nature of the aldol reactions between the solid enolate **2** and solid or liquid aldehydes in this study. First of all, the reaction mixture appeared to remain a solid during the entire reaction period. Even in the solid(enolate)-liquid(aldehyde) reactions, the mixture was still in the solid state appearing like liquid-wetted sand. Second, the reactions generally afforded low yields of ~10 to 30% because the extent of a heterogeneous reaction should be mainly limited by the contact area of reactants, providing that the aldolate products are still bonded to the surface of the enolate lattice and block further reactions. We have determined the chemical contents of the solid state reaction mixtures after quenching and found large amounts (>60%) of unchanged aldehyde reactants. For examples, the reaction of **2** with *o*-nitrobenzaldehyde at -78 °C for 4 h in the solid state yielded 17% of aldols based on the stoichiometry of the aldehyde and the unchanged *o*-nitrobenzaldehyde at the end of the reaction was found to be 80% by GLC analysis. Similarly, the solid state reaction of **2** with *o*-anisaldehyde at -20 °C for 4 h afforded the aldols in a 12% yield and the unchanged aldehyde was about 70%. Therefore, the low yields obtained in the solid state aldol reactions were due to the low conversions of the aldehydes. Since the enolate **2** was in excess in the reactants, the conversions of **2** were even lower than those of the aldehydes. Third, the yields of all the solid state reactions were found to have little dependence on the reaction time and temperature, again because of the contact surface area limitation. For the same reason, the yields of the reactions were also found to be influenced little by the stoichiometry of the solid reactants. For example, the solid state reactions of 1 equivalent of *p*-chlorobenzaldehyde with 1.2, 1.4 and 2 equivalents of the enolate **2** at 22 °C for 3 days gave similar low yields of aldol products, i.e. 22, 24 and 22%, respectively. Finally, using the same techniques as the aldol additions, we have also carried out asymmetric oxidation reactions of the lithium enolate **2** with enantiopure (+) or (-)- (camphorylsulfonyl)oxaziridines[42] both in THF solution and in the solid state.[43] In THF, the product, methyl 2-hydroxy-3,3-dimethylbutanoate, was optically active with an e.e. of 53 to 73% in good yields. The same reactions performed in the solid state afforded the product in low yields (15-20%), which had, however, *no measurable optical rotation* (i.e. ~0% e.e.). These observations seem to validate the experimental techniques employed in the solid state aldol reactions.

On the other hand, there are some evidence against the heterogeneity arguments. One problem is how the reactions between two solid reactants could afford yields as high as 31% (Table I, entry 2). Although the yields of reactions in the solid state are generally much lower than those in solution, these are still too high, considering that only a small fraction of the surfaces of the reactants might be in actual molecular contact. The observed high yields could be resulted from local melting at the interfaces of the reactants since aldol reaction is highly exothermic. Consequently, the reactions might have taken place in a fluid-like interfacial region and the crystal lattice of the enolate would also be disordered or modified. Therefore, the structure of actual reacting species in these reactions cannot be established reliably with the available data in this study. Currently, we are conducting further experiments to solve the above formidable but interesting problem.

CONCLUSIONS

We have described the first comparative study of the solid state and the THF solution aldol addition reactions of lithium enolate of methyl 3,3-dimethylbutanoate **2** with various aldehydes at different reaction temperatures and times. At higher temperatures and longer reaction times, the diastereoselection of the reactions

both in solid state and in THF are mainly thermodynamically controlled to afford the anti aldols as the predominate products. At lower temperatures and shorter times, the stereoselection of the both reactions are mainly kinetically controlled. The ratios of syn:anti isomers obtained from all the kinetically controlled reactions are approximately 50:50 except the reactions involving sterically small aldehydes, which give syn aldols as major products. In general, the solid state reactions afforded low yields while the yields of the solution reactions ranged from good to almost quantitative. The conversions of the aldehydes in the solid state reactions were also found to be low, in majority of cases ~20% and generally < 40%. The stereochemical outcomes can be interpreted satisfactorily using the Zimmerman-Traxler-Dubois transition state models with or without considering the involvement of aggregation of the enolate. The diastereoselectivity of all the aldol addition reactions in the solid state is approximately the same as that in THF solution. These results suggest that the same reacting species and transition state are involved in both the solid state and the solution reactions under our experimental conditions.

In addition, we have also attempted to identify the actual reacting enolate species in these reactions. Unfortunately, since we have not been able to substantiate whether the reactions in the solid state are truly heterogeneous at the microscopic level, *no definitive conclusion about the actual reacting species can be drawn in this study*. However, further investigation along this line might be proven fruitful in revealing the identity of the true reacting species and in reaching a better understanding of the fascinating chemistry of enolates.

EXPERIMENTAL SECTION

Materials and instrumentation. All glassware were oven dried at 125 °C for a minimum of 8 hours prior to assembly. All reactions were carried out in a dry argon atmosphere. THF (Fisher) and dioxolane (Aldrich) were distilled from sodium/benzophenone under argon atmosphere immediately prior to use. Fresh solutions of lithium diisopropylamide (LDA) in THF were prepared from 2.5 M *n*-BuLi solution in hexane (Aldrich) and diisopropylamine (Aldrich) at -20 °C. Methyl 3,3-dimethybutanoate (Lancaster) was distilled under reduced pressure prior to use. The aldehydes employed were purchased from Aldrich and were purified by either distillation or recrystallization. Enantioenriched D-(+)-2,3-isopropylidine glyceraldehyde was prepared from the reaction of D-mannitol (Aldrich) with 2,2-dimethoxypropane (Aldrich) followed by $NaIO_4$-oxidation, using the literature procedure.[32] Proton NMR spectra of the samples in $CDCl_3$ were recorded on a Bruker 250 FT-NMR spectrometer operating at 250 MHz. Chemical shifts in ppm were referenced to the residual protons of the solvent or to an internal tetramethylsilane (TMS) standard. Mass spectra were recorded as m/e on a Finnigan 4000 GC/MS using chemical ionization (CI) with methane as carrier and ionizing gas or electron impact (EI) technique, giving $(M+H)^+$ or $(M)^+$, respectively. Gas-liquid chromatography was performed on a Varian 3700 GC or on a Hewlett Packard 5890A GC connected to a Varian CDS 111 integrator. A packed glass column (Supelcoport 3% OV-17, 6' x 1/8", 80/100) or a capillary column (Supelco 2-4028, 30 m x 0.25 mm, SPB-1 phase) was employed for analysis. Analytical thin-layer chromatography (TLC) was performed using 2.5x10 cm (250 microns) precoated silica gel plates (Analtech). Preparative TLC (PTLC) was performed using 20x20 cm (1000 microns) silica gel plates (Analtech). The eluant used for TLC was methanol-benzene in a volume ratio of 5:95. Melting points were recorded on a Mel-Temp apparatus and were uncorrected. The optical rotations were measured at the wavelength of the sodium D line with $CHCl_3$ as solvent at 20 °C. All the yields reported were for the purified products and were calculated based on stoichiometry of the aldehyde employed. In general, the error margin for the values of the syn and anti contents was approximately ±5 based on parallel preparations and analyses by NMR and GLC. The yields could be reproduced generally within 10%.

General procedure for the aldol addition reaction of the lithium enolate of methyl 3,3-dimethylbutanoate (2) with aldehydes in THF. A 50-mL two-necked round bottomed flask was fitted with argon inlet and outlet, a rubber septum and a magnetic stirring bar. In the flask were placed 5 mL of freshly distilled THF and 0.42 mL (30 mmol) of dry diisopropylamine. The flask was then cooled to -20 °C and 1.2 mL (30 mmol) of a 2.5 M solution of *n*-BuLi in hexane were added via a syringe during 5 min. The reaction

mixture was stirred at -20 °C for 15 min to complete LDA formation. Upon further cooling the LDA solution to -78 °C with a dry ice-acetone bath, 0.39 mL (30 mmol) of methyl 3,3-dimethylbutanoate (Aldrich) was added over a period of 5 min. The solution was stirred at -78 °C for 90 min to afford the lithium ester enolate **2**. To this solution maintained at -78 °C (or other temperatures as specified in the text), 30 mmol of an appropriate aldehyde in ~5 mL of THF was added during 5 min. The extent of the reaction was monitored by TLC. After stirring for 4 h (or other time spans as specified in the text), the reaction mixture was quenched at -78 °C (or other specified temperatures) by adding 5 mL of saturated NH_4Cl aqueous solution in one portion, followed by 10 mL of diethyl ether about 3 min later. The mixture was warmed to, and maintaining for 15 min at, room temperature. The content was then transferred to a separatory funnel, where the organic layer was separated. The aqueous layer was further extracted with diethyl ether (2x10 mL). The combined organic extract was washed with 10 mL of saturated brine and was dried over anhydrous Na_2SO_4. Upon filtration and removal of the solvent at room temperature under reduced pressure, the crude aldol product was obtained. This crude aldol product was purified by preparative TLC. The purified product were characterized via ^{1}H-NMR, IR and Mass spectroscopy and GLC.

General procedure for the aldol addition reaction of the lithium enolate of methyl 3,3-dimethylbutanoate (2) with aldehydes in the solid state. The same procedure for preparation of the lithium enolate of methyl 3,3-dimethylbutanoate **2** in THF was employed to prepare solid lithium enolate. Thus, upon formation of the enolate **2** in THF solution at -78 °C, the solvent was removed in vacuo to afford the enolate as a white solid. The structure of **2** and the presence of THF in the solid **2** were verified by solution NMR spectroscopy. Prior to use, the solid enolate **2** was further dried thoroughly in vacuo at -20 °C until a fine, loose powder was obtained. This powdered lithium enolate was cooled to -78 °C (or other temperatures specified in the text) under a dry argon atmosphere. A freshly ground fine powder of appropriate aldehyde (0.83 equiv. or otherwise specified in the text) was added to the cooled enolate powder in argon. The contents were mixed thoroughly by shaking and by magnetic stirring and were held at -78 °C (or other specified temperatures) for 4 h (or otherwise specified). The contents remained solid during the entire reaction period before quenching with saturated NH_4Cl aqueous solution and ether. The quenching, isolation, purification and characterization of the products were carried out in the same manner as described in the solution reactions.

In the case of the reactions of the solid enolate with liquid aldehydes, the liquid aldehydes were added dropwise to the powdered enolate **2** at -78 °C in argon with agitation and magnetic stirring. The lithium enolate remained a solid (somewhat like wetted sand) in the presence of liquid aldehydes during the entire 4-hour reaction period at low temperature. However, at higher temperatures (e.g. 22 °C) the reaction mixture became a paste-like mass over a short period of time and the isolation of the aldol products was not achieved.

Aldol Reactions of 2 with Aldehydes at -78 °C for 4 h:

Methyl 2-*t*-butyl-3-(*o*-anisyl)-3-hydroxypropionate (entry 1, Table I). Yields of 94% from the THF solution reaction and of 29% from the solid state reaction; colorless oil: bp 135-137 (2 mm Hg); ^{1}H-NMR ($CDCl_3$) δ 1.0, 1.15 (2 s, 9 H, *t*-Bu), 2.6 (d, J = 3.3 Hz, anti HC(2)), 2.85(d, J =10.1 Hz, syn HC(2)), 3.2-3.95 (4 s, 6 H, -COOMe and -OMe), 4.2-5.1 (m, 2 H, -OH and HC(3)), and 6.8-7.4 (m, 4 H, Ph). IR (thin film) 3525, 2954, 1733, 1653, 1493, 1241, 1152, 1028, 755 cm^{-1}. MS: m/e 266 $(M)^+$; Calcd. for $C_{15}H_{22}O_4$: m/e 266. Anal. Cald: C, 67.67; H, 8.27. Found: C, 67.29; H: 8.01.

Methyl 2-*t*-butyl-3-(*p*-chlorophenyl)-3-hydroxypropionate (entry 2, Table I). Yields 73% in THF and 31% in the solid state; colorless oil: bp 128-130 °C (2 mm Hg); ^{1}H-NMR ($CDCl_3$) δ 0.95, 1.15 (2 s, 9 H, *t*-Bu), 2.45 (d, J =3.4 Hz, anti HC(2)), 2.6 (d, J =10 Hz, syn HC(2)), 3.2, 3.45 (2 s, 3 H, -COOMe), 4.05- 4.95 (m, 2 H, -OH and HC(3)), and 7.1-7.25 (m, 4 H, Ph). IR (thin film) 3484, 2955, 1733, 1653, 1490, 1436, 1367, 1257, 1198, 1155, 1090, 1014, 829 cm^{-1}. MS: m/e 272 $(M+H)^+$; Calcd. for $C_{14}H_{19}O_3Cl$: m/e 271. Anal. Calcd: C, 62.10; H, 7.07. Found: C, 61.84; H, 6.79.

Methyl 2-*t*-butyl-3-hydroxy-3-(*p*-nitrophenyl)propionate (entry 3, Table I). Yield 96% in THF and18% in the solid state; yellow viscous oil; ^{1}H-NMR ($CDCl_3$) δ 1.0, 1.1 (2 s, 9 H, *t*-Bu), 2.5 (d, J =

2.9 Hz, anti HC(2)), 2.65 (d, J=9.5 Hz, syn HC(2)), 3.2, 3.5 (2 s, 3H, -COOMe), 4.4-4.5 (m, 1 H, -OH), 5.1 (m, 1 H, HC(3)), and 7.4-8.1(m, 4 H, Ph). IR (thin film) 3484, 2956, 1728, 1605, 1522, 1347, 1156, 857 cm^{-1}. MS: m/e 282 $(M+H)^+$; calcd. for $C_{14}H_{19}NO_5$: m/e 281. Anal. Calcd: C, 59.79; H, 6.76. Found: C, 59.44; H, 6.55.

Methyl 2-*t*-butyl-3-hydroxy-3-(*m*-nitrophenyl)propionate (entry 4, Table I). Yield 98% in THF and12% in the solid state; yellow viscous oil; ^{1}H-NMR ($CDCl_3$) δ 1.0, 1.05 (2 s, 9 H, *t* -Bu), 2.5 (d, J=2.4 Hz, anti HC(2)), 2.6 (d, J =9.8 Hz, syn HC(2)), 2.7-2.8, 4.4 (bs, d, 1 H, J =8.94 Hz, -OH), 3.2, 3.5 (2 s, 3 H, -COOMe), 5.05 (d, 1 H, J =9.8 Hz, HC(3)), and 7.4-8.2 (m, 4 H, Ph). IR (thin film) 3487, 2956, 1733, 1618, 1534, 1350, 1146, 720 cm^{-1}. MS: m/e 282 $(M+H)^+$; calcd. for $C_{14}H_{19}NO_5$: m/e 281. Anal. Calcd: C, 59.79; H, 6.76. Found: C, 59.44; H, 6.52.

Methyl 2-*t*-butyl-3-hydroxy-3-(*o*-nitrophenyl)propionate (entry 5, Table I). Yield 97% in THF and17% in the solid state; yellow viscous oil; ^{1}H-NMR ($CDCl_3$) δ 1.0, 1.1 (2 s, 9 H, *t* -Bu), 2.6 (d, J = 1.8 Hz, anti HC(2)), 2.8 (d, J =10.1Hz, syn HC(2)), 3.2, 3.4 (2 s, 3 H, -COOMe), 4.8 (d, 1 H, J = 9.8 Hz, -OH), 5.7 (d, 1 H, J =9.7 Hz, HC(3)), and 7.3-8.0 (m, 4 H, Ph). IR (thin film) 3476, 2956, 1732, 1706, 1608, 1529, 1351, 1202, 1156, 857, 742 cm^{-1}. MS: m/e 282 $(M+H)^+$; calcd. for $C_{14}H_{19}NO_5$: m/e 281. Anal. Calcd: C, 59.79; H, 6.76. Found: C, 59.73; H, 6.61.

Methyl 2-*t*-butyl-3-hydroxy-3-(5-nitro-2-furyl)propionate (entry 6, Table I). Yield 58% in THF and10% in the solid state; yellow viscous oil; ^{1}H-NMR ($CDCl_3$) δ 1.1 (2 s, 9 H, *t* -Bu), 2.7 (d, J =2.9 Hz, anti HC(2)), 2.85-2.9 (d, J = 9.3 Hz, syn HC(2)), 3.6, 3.7 (2 s, 3 H, -COOMe), 4.5 (d, 1 H, J = 9.7 Hz, -OH), 5.1-5.2 (m, 1 H, HC(3)), and 6.5-7.3(m, 2 H, furyl). IR (thin film) 3461, 2961, 1780, 1733, 1652, 1558, 1496, 1436, 1354, 1156, 943, 878, 812 cm^{-1}. MS: m/e 272 $(M+H)^+$; calcd. for $C_{12}H_{17}NO_6$: m/e 271. Anal. Cald: C, 53.14; H, 6.27. Found: C, 53.11; H, 6.17.

Methyl 2-*t*-butyl-3-hydroxy-3-(5-nitro-2-thienyl)propionate (entry 7, Table I). Yield 66% in THF and19% in the solid state; orange oil; ^{1}H-NMR ($CDCl_3$) δ 1.05–1.1 (2s, 9 H, *t* -Bu), 2.65 (d, J =2.3 Hz, anti HC(2)), 2.65-2.7 (d, J =9.6 Hz, syn HC(2)), 3.5, 3.65 (2 s, 3 H, -COOMe), 3.2, 4.7 (bs, d, 1 H, J = 9.9 Hz, -OH), 5.2-5.3 (2 d, 1 H, J =9.9 Hz, HC(3)), and 6.8-7.8(m, 2 H, thienyl). IR (thin film) 3480, 2957, 1733, 1652, 1539, 1506, 1436, 1340, 1260, 1197, 1156, 816, 734 cm^{-1}. MS: m/e 288 $(M+H)^+$; calcd. for $C_{12}H_{17}NO_5S$: m/e 287. Anal. Cald: C, 50.17; H, 5.92. Found: C, 50.30; H, 5.86.

Methyl 2-*t*-butyl-3-hydroxy-3-phenylpentanoate (Scheme 2). Yield 70% in THF and 12% in the solid state; colorless oil: bp 120-122° C (2 mmHg); ^{1}H-NMR ($CDCl_3$) δ 0.95, 1.0, 1.15 (3 s, 9 H, *t*-Bu), 1.3, 1.35 (2 d, 3 H, J =4.4 Hz, Me), 2.2-2.3 (m, 1 H, HC(4)), 2.5-2.8 (m, 1 H, HC(2)), 3.6-3.75 (3 s, 3 H, -COOMe), 3.8-4.15 (m, 2 H, HC(3), OH), and 7.1-7.35 (m, 5 H, Ph). IR (thin film) 3502, 2956, 1707, 1652, 1495, 1367, 1266, 1157,1010, 761 cm^{-1}. MS: m/e 265 $(M+H)^+$; calcd. for $C_{16}H_{24}O_3$: m/e 264. Anal. Calcd: C, 72.72; H, 9.09. Found: C, 72.35; H, 9.25.

Methyl 2-*t*-butyl-4,5-isopropylidinedioxy-3-hydroxypentanoate. Yield 50% in THF and 6% in the solid state; colorless viscous oil; ^{1}H-NMR ($CDCl_3$) δ 0.95, 1.1 (4 s, 9 H, *t*-Bu), 1.2- 1.35 (4 s, 6 H, 2 x Me), 2.2-2.5 (m, 1 H, HC(2)), 2.65 (s, 1 H, -OH), 3.6-3.7 (3 s, 3 H, -COOMe), and 3.8-4.2 (m, 4 H, HC(3), HC(4), and $-CH_2-$ at C(5)). IR (thin film) 3493, 2956, 1734, 1652, 1456, 1370, 1258, 1158, 1088 cm^{-1}. MS: m/e 261 $(M+H)^+$; calcd. for $C_{13}H_{24}O_5$: m/e 260. Anal. Cald: C, 59.98; H, 9.29. Found: C, 60.37; H, 9.39.

The aldol reactions at 22 °C in THF for 4 h and in the solid state for 72 h (Table II) afforded the same products as described above, except that the syn:anti ratios were different. Methyl 2-*t*-butyl-3-(*o*-anisyl)-3-hydroxypropionate (entry 1, Table II), methyl 2-*t*-butyl-3-hydroxy-3-(*p*-nitrophenyl)propionate (entry 3, Table II) and methyl 2-*t*-butyl-3-hydroxy-3-(*o*-nitrophenyl)propionate (entry 5, Table II) were isolated as solids with melting points of 70-71, 72-73 and 77-78 °C, respectively, after recrystallization from *n*-pentane or *n*-hexane.

Aldol Reactions of 2 with Liquid Aldehydes at -78 °C for 4 h:

Methyl 2-*t*-butyl-3-hydroxybutanoate (entry 1, Table III). Yield 92% in THF and 29% in the

solid state; colorless liquid: bp 52-53 °C (2 mmHg); ^{1}H-NMR ($CDCl_3$) δ 1.1 (2 s, 9 H, *t*-Bu), 1.25 (d, 3 H, *J*=6.2 Hz, 3-Me), 2.2 (m, anti HC(2)), 2.35 (d, *J* = 8.5 Hz, syn HC(2)), 2.85 (bs, 1 H, -OH), 3.7-3.75 (2 s, 3 H, -COOMe), and 4.1-4.2 (m, 1 H, HC(3)). IR (thin film) 3447, 2958, 1734, 1652, 1456, 1365, 1262, 1155, 1008 cm^{-1}. MS: m/e 175 $(M+H)^+$; calcd. for $C_9H_{18}O_3$: m/e 174. Anal. Calcd: C, 62.07; H, 10.35. Found: C, 61.64; H, 10.44.

Methyl 2-*t*-butyl-3-hydroxypentanoate (entry 2, Table III). Yield 90% in THF and 39% in the solid state; colorless liquid: bp 72-73 °C (2 mm Hg); ^{1}H-NMR ($CDCl_3$) δ 0.85-0.9 (t, 3 H, CH_3 at C_5), 1.0 (2s, 9 H, *t*-Bu), 1.2-1.4 (m, 2 H, CH_2 at C_4) 1.8 (bs, 1 H, -OH), 2.2 (d, *J*=2.1 Hz, anti HC(2)), 2.35 (d, *J* = 8.8 Hz, syn HC(2)), 3.6, 3.7 (2 s, 3 H, -COOMe), and 3.75-3.9 (m, 1 H, HC(3)). IR (thin film) 3510, 2965, 1734, 1652, 1456, 1381, 1100, 803 cm^{-1}. MS: m/e 189 $(M+H)^+$; calcd. for $C_{10}H_{20}O_3$: m/e 188. Anal. Calcd: C, 63.83; H, 10.64. Found: C, 63.42; H, 10.57.

Methyl 2-*t*-butyl-3-hydroxyhexanoate (entry 3, Table III). Yield 85% in THF and 30% in the solid state; colorless liquid: ^{1}H-NMR ($CDCl_3$) δ 0.9-1.6 (m, 7 H, *n*-Pr at C_3), 1.0 (2 s, 9 H, *t*-Bu), 1.8 (bs, 1 H, -OH), 2.2 (m, anti HC(2)), 2.3 (d, *J*=8.6 Hz, syn HC(2)), 3.6, 3.7 (2 s, 3 H, -COOMe), and 3.8-4.0 (m, 1 H, HC(3)). IR (thin film) 3432, 2961, 1733, 1652, 1456, 1398, 1184 cm^{-1}. MS: m/e 203$(M+H)^+$; calcd. for $C_{11}H_{22}O_3$: m/e 202. Anal. Calcd: C, 65.35; H, 10.89. Found: C, 64.78; H, 10.63.

Methyl 2-*t*-butyl-3-hydroxy-4-methylpentanoate (entry 4, Table III). Yield 88% in THF and 35% in the solid state; colorless liquid: bp 56-57 °C (2 mmHg); ^{1}H-NMR ($CDCl_3$) δ 0.85-0.98 (4d, 6 H, 2 x CH_3 at C_4), 1.0-1.1 (2 s, 9 H, *t*-Bu), 1.5-1.65 (m, 1 H, C_4H), 2.35 (d, *J*=1.8 Hz, anti HC(2)), 2.35-2.4 (d, *J*=10.3 Hz, syn HC(2)), 3.45 (bs, 1 H, -OH), 3.6, 3.7 (2 s, 3 H, -COOMe), and 3.85 (m, 1 H, HC(3)). IR (thin film) 3480, 2959, 1734, 1652, 1558, 1368, 1156, 1003 cm^{-1}. MS: m/e 203$(M+H)^+$; calcd. for $C_{11}H_{22}O_3$: m/e 202. Anal. Calcd: C, 65.35; H, 10.89. Found: C, 65.86; H, 11.19.

Methyl 2-*t*-butyl-3,3-dimethyl-3-hydroxypentanoate (entry 5, Table III). Yield 81% in THF and 23% in the solid state; white solid (recrystallization from *n*-pentane): mp 87-88 °C; ^{1}H-NMR ($CDCl_3$) δ 0.95 (2 s, 9 H, 3-*t*-Bu), 1.1 (2 s, 9H, 2-*t*-Bu), 1.45 (bs, 1 H, -OH), 2.35-2.4 (2 d, *J* =2.2 Hz, anti and syn HC(2)), 3.6 (2 s, 3 H, -COOMe), and 3.85-3.9 (2 d, 1 H, HC(3)). IR (KBr) 3518, 2951, 1716, 1485, 1436, 1361, 1209, 1159, 1075, 998 cm^{-1}. MS: m/e 217 $(M+H)^+$; calcd. for $C_{12}H_{24}O_3$: m/e 216. Anal. Calcd: C, 66.67; H, 11.11. Found: C, 67.15; H, 10.78.

Methyl 2-*t*-butyl-3-hydroxy-3-phenylpropionate (entry 6, Table III). Yield 93% in THF and 31% in the solid state; colorless liquid; ^{1}H-NMR ($CDCl_3$) δ 0.95, 1.15 (2 s, 9 H, *t*-Bu), 2.55 (d, *J* = 3.8 Hz, anti HC(2)), 2.65 (d, *J* =9.9 Hz, syn HC(2)), 3.2, 3.45 (2 s, 3 H, -COOMe), 3.85 (m, 1 H, -OH), 4.95 (m, 1 H, HC(3)), and 7.15-7.25 (m, 5 H, Ph). MS: m/e 237 $(M+H)^+$; calcd. for $C_{14}H_{20}O_3$: m/e 236. All the spectroscopic data agree well with those in the literature[44].

Methyl 2-*t*-butyl-3-(2-furyl)-3-hydroxypropionate (entry 7, Table III). Yield 95% in THF and18% in the solid state; colorless viscous oil; ^{1}H-NMR ($CDCl_3$) δ 0.95, 1.0 (2 s, 9 H, *t*-Bu), 2.7 (d, *J* = 4.9 Hz, anti HC(2)), 2.85-2.9 (d, *J* =10.0 Hz, syn HC(2)), 3.4, 3.6 (2 s, 3 H, -COOMe), 4.95 (m, 1 H, HC(3)), and 6.2-6.3, 7.4 (m, s, 3 H, furyl). IR (thin film) 3500, 2960, 1733, 1652, 1558, 1436, 1370, 1157, 912, 733 cm^{-1}. MS: m/e 228 $(M+H)^+$; calcd. for $C_{12}H_{19}O_4$: m/e 227. Anal. Calcd: C, 63.72; H, 7.97. Found: C, 63.11; H, 7.78.

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