# Asymmetric Aldol Reactions. A Titanium Enolate Giving Very High Diastereofacial Selectivities

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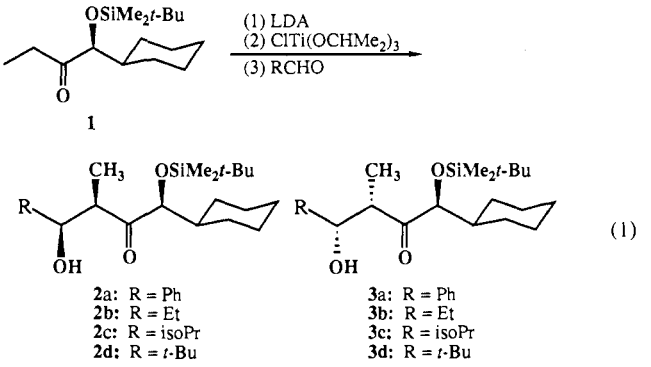
**Abstract:** Diastereofacial selectivities of 99% can be conveniently obtained in aldol reactions of the chiral titanium enolate derived from the ketone $C_2H_5COCH(OSiMe_2$-*t*-Bu)-*c*-$C_6H_{11}$, with representative aldehydes. The key to obtaining such selectivities is shown to be use of excess titanium reagents (≥2 mol equiv) to prevent interference by the lithium salt formed when titanium enolates are, as usual, generated via the corresponding lithium enolates. Low cost, low toxicity, and ease of workup should make titanium enolates especially appealing to synthetic chemists. We have discovered a surprising similarity between aldol reactions employing the traditional titanium reagent $ClTi(OCHMe_2)_3$ and the very inexpensive and easily handled reagent $Ti(OCHMe_2)_4$. These reagents now provide a very useful method for synthesis of chirally pure *syn*-β-hydroxy-α-methylcarboxylic acids.

Titanium(IV) enolates should have very interesting properties since titanium is a transition metal. There is evidence of chelation control in certain reactions of Ti(IV) species, and 6- and even 8-coordinate complexes are known.[1,2] Titanium could very possibly give bridged transition structures with locked geometries, thus generating precise stereocontrol. Moreover, titanium alkoxide reagents have advantages of low cost, ease of workup, and hydrolysis to nontoxic $TiO_2$. We aim to exploit and explain these potential advantages of titanium reagents for organic synthesis.

Aldol reactions of titanium enolates had not previously given exceptional stereocontrol,[1] yet current models of aldol transition structures[3-5] led us to conclude that high levels should be attainable. Consequently, our first goal was to prove that titanium-mediated aldol reactions can indeed produce diastereofacial selectivities approaching 99%.

Only a few examples of aldol reactions of titanium enolates have been reported.[1,6-8] Most of the uses of titanium have involved addition reactions to aldehydes and ketones of either alkyltitanium reagents or silyl enol ethers using titanium as the Lewis acid (Mukaiyama aldol addition).[1,9] Of the few examples of diastereofacial selectivity reported for titanium aldol reactions, all but three[10-12] involve additions to chiral alkoxy or silyloxy aldehydes or ketones.[13-15] The selectivities observed in these cases were ≤93%, except for one report of 99%,[15] which appeared after our initial work.[16]

Here we detail the results of our extensive investigations on titanium-mediated aldol reactions[16] of chiral ketone **1**[17] (eq 1)



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culminating finally in 99% diastereofacial selectivities, as well as our discovery that the inexpensive reagent $Ti(OCHMe_2)_4$ gives highly selective aldol reactions. These titanium-mediated aldol reactions are thus shown to be as diastereofacially selective as the reported[17] boron-mediated ones.

## Results

We have studied the aldol reactions of representative aldehydes with the titanium and lithium enolates of **1**. Stereochemical analysis provided diastereofacial selectivities, syn products (**2** and **3**) being formed exclusively.

**Stereochemical Assignments of Aldol Products.** The stereochemical assignments for the major products from the reactions with benzaldehyde, propionaldehyde, and isobutyraldehyde (**2a-c**) were made by comparison of their $^1H$ NMR spectra with the chemical shifts reported by Masamune et al.[17] In view of the opposite stereochemistry obtained in a related reaction of a lithium enolate,[18] we also corroborated the stereochemistry of **2a** with an X-ray crystal structure of its 4-nitrobenzoate derivative. The stereochemistry of the previously unreported aldol product from pivalaldehyde (**2d**) was shown by X-ray analysis of the corresponding 1,4-diol to be the same as that of the other products.

**Diastereofacial Selectivities.** We have developed conditions giving very high diastereofacial selectivities in these titanium-mediated aldol reactions (Table I). In contrast, the lithium enolate gave modest selectivities (Table I). In the course of

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**Table I.** Aldol Reactions of Ketone **1**

| aldehyde | metal (M) [equiv][a] | molarity (**1**) | ratio of **2**:**3**[b] |
|---|---|---|---|
| PhCHO | Li | 0.17 | 1.2:1 |
| | $Ti(OCHMe_2)_3$ [1.0] | 0.17 | 6.5:1 |
| | $Ti(OCHMe_2)_3$ [2.5] | 0.17 | 67:1 |
| | $Ti(OCHMe_2)_3$ [3.0] | 0.17 | 76:1 (±2.6)[c,d] |
| | $Ti(OCHMe_2)_3$ [3.0] | 0.08 | 72:1 |
| | $Ti(OCHMe_2)_3$ [4.0] | 0.17 | 38:1 (±5.5)[e] |
| | $Ti(OCHMe_2)_3$ [1.0] | 0.17 | 46:1[f] |
| EtCHO | Li | 0.17 | 4:1 (±0.7)[e] |
| | $Ti(OCHMe_2)_3$ [1.0] | 0.17 | 29:1 (±3.7)[c] |
| | $Ti(OCHMe_2)_3$ [3.0] | 0.17 | 27:1 |
| | $Ti(OCHMe_2)_3$ [3.0] | 0.08 | 71:1 |
| | $Ti(OCHMe_2)_3$ [4.0] | 0.17 | 53:1 (±11.5)[e] |
| | $Ti(OCHMe_2)_3$ [4.0] | 0.08 | 114:1 (±11.5)[e] |
| | $Ti(OCHMe_2)_3$ [1.0] | 0.17 | 29:1[f] |
| $Me_2CHCHO$ | Li | 0.17 | 3:1 |
| | $Ti(OCHMe_2)_3$ [1.0] | 0.17 | 3:1 |
| | $Ti(OCHMe_2)_3$ [1.5] | 0.17 | 3:1 (±0.7)[e] |
| | $Ti(OCHMe_2)_3$ [1.75] | 0.17 | 74:1 |
| | $Ti(OCHMe_2)_3$ [2.0] | 0.17 | 75:1 |
| | $Ti(OCHMe_2)_3$ [3.0] | 0.17 | 95:1 (±2.0)[e] |
| | $Ti(OCHMe_2)_3$ [3.0] | 0.08 | 138:1 (±1.0)[c] |
| | $Ti(OCHMe_2)_3$ [4.0] | 0.17 | 64:1 (±1.5)[e] |
| | $Ti(OCHMe_2)_3$ [1.0] | 0.17 | 100:1[f] |
| $Me_3CCHO$ | Li | 0.17 | 1:1.5 |
| | $Ti(OCHMe_2)_3$ [3.0] | 0.17 | ≥117:1 |

[a] Equivalents refer to the amount of $ClTi(OCHMe_2)_3$ (based on *n*-butyllithium) used to generate the titanium enolate from the lithium enolate. [b] Ratios were determined by integration of $^1H$ NMR of the crude product mixture for benzaldehyde and trimethylacetaldehyde adducts and by $^{19}F$ NMR of the trifluoroacetates for the propionaldehyde and isobutyraldehyde adducts. Isolated yields of aldol products **2** were from 75–88% (isolations not fully optimized). [c] Standard deviation of three or more runs. [d] This ratio expressed as percent is 98.7% and thus rounds to a 99% level of selectivity. [e] Average deviation of two runs. [f] 1.0 equiv of 12-crown-4 added.

discovering these conditions, we have documented a remarkable, adverse lithium effect on stereoselectivity, which can, however, be prevented by use of excess titanium. In addition, we disclose our recent discovery that the less expensive and more stable reagent $Ti(OCHMe_2)_4$ gives very high selectivities when used in place of $ClTi(OCHMe_2)_3$, the reagent heretofore used in most titanium-mediated aldol reactions (Table II). If $Ti(OCHMe_2)_4$ proves to be generally useful (under investigation), it will be a very simple and practical reagent for aldol technology.

The ratios for aldol adducts **2a**:**3a** and **2d**:**3d** were determined by integration of the crude $^1H$ NMR spectra. Adducts **2b**:**3b** and **2c**:**3c** were first converted to their corresponding trifluoroacetates. $^{19}F$ NMR was then used to determine their selectivities.[19] This type of analysis is very similar to that used by Dale and Mosher[20] to determine optical purity of chiral alcohols and amines. To ensure that this conversion went to completion and no side reactions (possible racemization of carbinol center to give an anti product or elimination of water) occurred, a $^1H$ NMR of the trifluoroacetates was always taken. Fortunately, none of these possible complications arose.

Table I documents the most interesting discovery of this work. The selectivity for $ClTi(OCHMe_2)_3$-mediated reactions of representative aldehydes is dramatically improved by addition of an excess of the titanium reagent. The increase is most evident in the case of the isobutyraldehyde reactions, where a 30-fold increase in diastereofacial selectivity is seen in comparing 3.0 equiv to 1.0 equiv of $ClTi(OCHMe_2)_3$. The other aldehydes studied, benzaldehyde and propionaldehyde, also show increases that are substantial (12- and 2-fold, respectively) but not as dramatic as for isobutyraldehyde. The ratios obtained with excess titanium reagent are also mimicked by the addition of a crown ether,

**Table II.** Aldol Reactions of Ketone **1** Using $Ti(OCHMe_2)_4$

| aldehyde | equiv of $Ti(OCHMe_2)_4$[a] | molarity (**1**) | ratio of **2**:**3**[b] |
|---|---|---|---|
| PhCHO | 1.0 | 0.08 | 2.7:1 (±0.0)[c] |
| | 3.0 | 0.08 | 44:1 (±15)[d] |
| | 3.0 | 0.04 | 71:1 (±1.0)[c] |
| | 4.0 | 0.04 | 68:1 |
| EtCHO | 1.0 | 0.08 | 10:1 (±4.0)[c] |
| | 3.0 | 0.08 | 52:1 |
| | 4.0 | 0.08 | 60:1 (±3.0)[c] |
| | 5.0 | 0.04 | 67:1 (±4.5)[d] |
| $Me_2CHCHO$ | 1.0 | 0.08 | 2.6:1 (±0.3)[c] |
| | 3.0 | 0.08 | 50:1 (±11)[c] |
| | 3.0 | 0.04 | 55:1 |
| | 4.0 | 0.04 | 66:1 (±7.8)[d] |

[a] Equivalents refer to the amount of $Ti(OCHMe_2)_4$ (based on *n*-butyllithium) used to generate the titanium enolate from the lithium enolate. [b] Ratios were determined as before (Table I). For each aldehyde the best observed selectivity, expressed as percent, is >98.5%, and all thus round to 99%. [c] Average deviation of two runs. [d] Standard deviation of three or more runs.

12-crown-4, which selectively complexes the lithium cation.[21-23] An experiment in which the relative amounts of LDA and ketone were varied also indicates that lithium and not some need for an excess of titanium causes the lower selectivities with 1 equiv of $ClTi(OCHMe_2)_3$. In a reaction with isobutyraldehyde, a 2.3 equiv excess of $ClTi(OCHMe_2)_3$ with respect to the ketone **1**, but only 1.5 equiv with respect to LDA originally added, gave a **2c**:**3c** ratio of only 2.7:1. Since 12-crown-4 is more expensive than $ClTi(OCHMe_2)_3$ and hampers separation of products, while excess titanium reagent is readily removed upon workup, use of excess titanium reagent is the convenient method of choice.

Diastereofacial selectivities for titanium-mediated reactions improved significantly at lower concentrations. With propionaldehyde a >2-fold increase in selectivity resulted (3.0 or 4.0 equiv of $ClTi(OCHMe_2)_3$) upon lowering the ketone concentration from 0.17 to 0.08 M. With isobutyraldehyde a slightly lower increase (ca. 1.5-fold) was seen. Surprisingly, this dilution effect was not seen with benzaldehyde: the ratio stays the same within experimental error. These selectivity increases were achieved without significant increases in reaction times.

We also carried out aldol reactions employing $Ti(OCHMe_2)_4$ as the titanium reagent. One purpose of these experiments was to investigate whether a lithium titanium–ate enolate complex of the type $Li^+C{=}COTi^-(OCHMe_2)_4$ was plausible as a cause of the lower selectivity with 1.0 equiv of $ClTi(OCHMe_2)_3$. Although several titanium–ate complexes have been postulated,[24-26] the exact nature of this type of species is not known. They are reported to arise when $Ti(OCHMe_2)_4$ is added to a lithium enolate.[24,25] We postulated that a similar species with a chlorine replacing an isopropoxide ligand could be involved in the less selective reactions observed with 1.0 equiv of $ClTi(OCHMe_2)_3$. If so, $Ti(OCHMe_2)_4$ might behave much like $ClTi(OCHMe_2)_3$.

The reactions of $Ti(OCHMe_2)_4$ do indeed act very much like those of $ClTi(OCHMe_2)_3$, exhibiting an increase in selectivity in comparing 1.0 equiv with ≥3 equiv of $Ti(OCHMe_2)_4$. This increase is again most dramatic with isobutyraldehyde (19-fold) and is lower with benzaldehyde and propionaldehyde (16- and 5-fold, respectively). These reactions differ in three ways from the $ClTi(OCHMe_2)_3$ reactions, however. Completely opposite to the previous results, only the benzaldehyde $Ti(OCHMe_2)_4$-mediated aldol reaction shows an increase in ratio upon dilution. The best selectivity achieved for the aliphatic aldehydes (iso-

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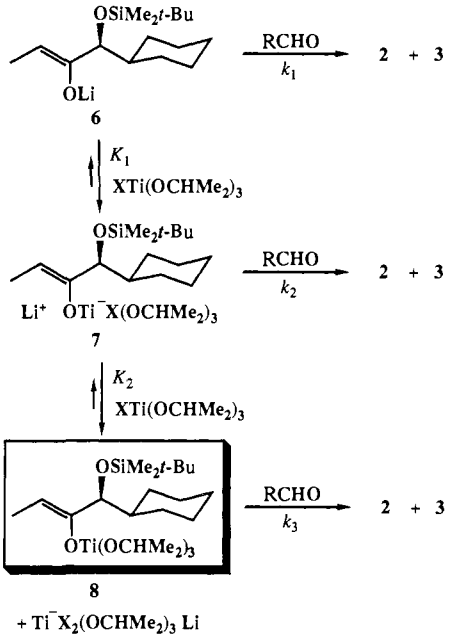
**Scheme I**




butyraldehyde and propionaldehyde) with $Ti(OCHMe_2)_4$ is significantly lower than the ratios achieved with $ClTi(OCHMe_2)_3$. The $Ti(OCHMe_2)_4$ reaction was unsuccessful with pivalaldehyde. No reaction was observed under the conditions described for the $ClTi(OCHMe_2)_3$-mediated aldol reactions or at a reaction temperature 10 °C higher (−20 to −30 °C).

## Discussion

The target of this investigation was to demonstrate that titanium-mediated aldol reactions of chiral ketones can produce diastereofacial selectivities approaching 99%. We have now shown that reactions of the chosen chiral ketone **1** with representative aldehydes do indeed meet this target. In doing so, we discovered novel phenomena associated with the nature and amount of the titanium reagent used.

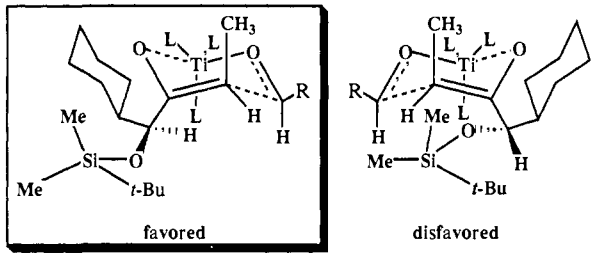
Only two aldol reactions of chiral titanium enolates had been reported[10,11] prior to our work.[16,27] Other than our results, very few diastereofacially selective aldol reactions of titanium enolates have been reported to date.[10-15] In only one case, which appeared after our original work,[16] did the stereoselectivity reach a level of 99%.[15]

We have determined the conditions for optimal control of diastereofacial selectivity. The resulting titanium-mediated aldol methodology is very useful. Low cost, low toxicity, and ease of handling[1,28,29] should make such aldol reactions especially appealing to synthetic chemists. The aldol products can be converted to *syn*-β-hydroxy-α-methylcarboxylic acids in high yields via desilylation and oxidation of the resulting α-hydroxyketone.[17]

A most interesting, previously unreported discovery made during this investigation is that use of excess titanium reagent in the generation of titanium enolates dramatically improves the diastereofacial selectivity and provides the key to obtaining 99% levels. Our data show that the high selectivity induced by excess titanium is actually dependent on lithium introduced by use of LDA for enolization. In reactions mediated by only 1 equiv of titanium, diastereofacial selectivities for branched aldehydes were low, but they increased dramatically upon addition of 1 equiv of 12-crown-4, a crown ether specific for lithium.[21-23] Some of the previous work on aldol reactions of titanium enolates generated via lithium enolates should be reconsidered in the light of our results.

We have further discovered that aldol reactions mediated by $Ti(OCHMe_2)_4$ yield nearly the same stereoselectivities as those mediated by $ClTi(OCHMe_2)_3$. Although there are differences (as would be expected), when a comparison is made between the two reagents under the same conditions, the ratios differ by 2-fold or less. In fact, these two reagents have striking similarities. Besides the similar stereoselectivities, both also give increased selectivity with the use of excess of titanium reagent and both give a greater increase for the larger aldehydes. Surprisingly, pivalaldehyde is unreactive (or very slow) with $Ti(OCHMe_2)_4$, even though it reacts in the presence of $ClTi(OCHMe_2)_3$. To our knowledge, the use of $Ti(OCHMe_2)_4$ in diastereofacially selective aldol reactions has never previously been reported. These results suggest that use of $Ti(OCHMe_2)_4$ as a very inexpensive and easily handled reagent for titanium-mediated aldol reactions is worthy of further exploration.

**Mechanistic Implications.** A nonchelated chairlike transition structure, **4**, analogous to that proposed for the corresponding boron enolate[17,30] best explains our data. Chelation of titanium

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to the α-siloxy group of the enolate is an a priori possibility. The opposite stereochemistry was observed for the analogous lithium enolate of $CH_3CH_2C(=O)CH(OSiMe_3)CMe_3$, and chelation of the (trimethylsilyl)oxy oxygen to Li was postulated.[18] The chair model could involve chelation only in a transition structure analogous to **5**, which does give opposite stereochemistry compared with **4**. It appears from models that the bulk of the (*tert*-butyldimethylsilyl)oxy group in ketone **1** is too great to permit chelation, so that **4** is preferred. Our data show that, with ketone **1**, even lithium, which does not have the bulky ligands present on titanium, gives the same preferred diastereomer as Ti, though with lowered diastereofacial selectivity. A similar effect, the presence of a bulky silyloxy group preventing chelation with titanium reagents, has been reported for titanium ester enolate aldol additions to α-silyloxy ketones.[15] Putative open transition structures may give syn products,[14,31,32] but the strong oxygen-coordinating ability of titanium makes open structures unlikely in the present case.

The simplest model that accounts for the lithium effect observed in these aldol reactions is outlined in Scheme I. The basic supposition is that equilibrium with either a lithium enolate (**6**) or a lithium titanium–ate enolate complex (**7**) causes the lower selectivites with 1.0 equiv of $ClTi(OCHMe_2)_3$ via less selective routes $k_1$ or $k_2$. A lithium *methyl*titanium–ate complex analogous to **7** has been proposed.[26] Assuming rapid prior equilibria and rate-determining transition structures involving C–C bond formation, the fraction of aldol products formed by each route ($k_1$, $k_2$, $k_3$) is determined only by the relative stability of the transition structure for that route (Curtin–Hammett principle[33,34]). The actual amount of the lithium enolate (**6**) is expected to be small,

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but its high reactivity could still make the transition structure for $k_1$ stable enough to contribute significantly to product formation. No kinetic data exist as yet for these aldol reactions, but reactions of lithium enolates with aldehydes are often complete in seconds at −78 °C in ether solvents at concentrations of 0.5 M.[35] In the case of ketone **1**, we have observed that the lithium-mediated aldol reaction with benzaldehyde at −78 °C is rapid, >98% complete in less than 15 min, while the corresponding titanium-mediated reaction (1.0 or 3.0 equiv) at −78 to −65 °C is less than 50% complete after 3 h (by $^1$H NMR based on **1** in each case). The relative stabilities of the transition structures for the $k_2$ and $k_3$ routes are subject to opposing effects: since the $k_2$ transition structure has a more electron-rich titanium center than that for $k_3$, the $k_2$ enolate moiety would be more nucleophilic toward the aldehyde carbonyl carbon, favoring $k_2$, but the $k_3$ titanium would be more electrophilic (a stronger Lewis acid) toward the aldehyde carbonyl oxygen, favoring $k_3$. For these reasons, it is not possible to predict which of the three routes should be preferred.

The effects of excess titanium and of 12-crown-4 can be explained with this model, using either **6** or **7** as the species producing the lower selectivities with 1 equiv of $ClTi(OCHMe_2)_3$. The excess of titanium reagent could serve to drive the equilibrium sufficiently to the titanium enolate (**8**) side to nearly preclude product formation via the lithium species ($k_1$) or the lithium–ate complex ($k_2$). Similarly, 12-crown-4 would drastically reduce product formation via both the $k_1$ and $k_2$ routes by removing lithium and its counterion (chloride in this case), which precipitate from the reaction mixture. The lithium enolate and the ate enolate complex would then be present in extremely small concentrations, and the enolate would be present almost entirely as free titanium enolate (**8**).

The fact that propionaldehyde gives a high selectivity even with only 1 equiv of titanium present (Table I) is easily explained when it is realized that the observed selectivity depends on the relative rates of the aldol reaction of **6** or **7** as compared to **8**. Because of the large steric requirement of titanium and its ligands in the aldol transition structure as compared with lithium, it is reasonable to assume that bulky aldehydes would retard the reaction rate of **8** more than that of **6**. Likewise, the more nucleophilic, electron-rich enolate moiety in the ate complex **7** might give a looser, more reactant-like transition structure, so that bulky aldehydes would also retard the reaction rate of **8** more than that of **7**. These effects should result in an increase in the ratio $k_1$:$k_3$ or $k_2$:$k_3$ as one goes from the smaller aldehyde to bulkier aldehydes. Consequently, with the smaller aldehyde (propionaldehyde) the ratio could be small enough that the products would arise mainly via $k_3$, from the highly selective species **8**. The branched aldehydes would cause the ratio to be larger, and a significant fraction of the products would arise via $k_1$ or $k_2$, from the less selective species **6** or **7**.

Because they can be explained either way, the results discussed so far do not allow us to distinguish with certainty between **6** or **7** as the cause of the lower ratios with 1 equiv of the titanium reagent. However, a corresponding effect of excess titanium was subsequently observed in an extensive study of the titanium-mediated aldol reactions of chiral *N*-acyloxazolidinones in our laboratories.[27] In those reactions the lower selectivities observed with 1.0 equiv of $ClTi(OCHMe_2)_3$ could not be adequately explained by the participation of a lithium enolate, and an ate complex analogous to **7** was proposed.

There is one piece of evidence from the present results that also supports the ate complex mechanism. The abrupt change of selectivity observed for isobutyraldehyde on going from 1.5 to 1.75 equiv of Ti can best be explained if the ate complex **7** is the source of the lower selectivities and $K_2 \gg 1$.[36] More data will be required to establish this mechanism firmly, but the weight of evidence so far indicates that it is the presence of the ate complex **7** (or a closely related species) that causes lowered selectivities.

We have considered a third possible lithium species leading to lower selectivity with 1 equiv of $ClTi(OCHMe_2)_3$. One can imagine an open chain transition structure involving a titanium enolate and a lithium-coordinated aldehyde. Molecular models of the four possible transition structures of this type suggest a preference for anti aldol products in this case. The fact that no anti product was detected in any of the cases studied probably rules out this transition structure as a major factor in determining any of the observed selectivities.

The source of the increase in selectivity upon running the reaction at higher dilution is unknown as yet. It is a real effect, as the increase is much larger than any experimental error. Conceivably, the cause for this increase is also a factor in the decreased selectivities for benzaldehyde and isobutyraldehyde upon going from 3 to 4 equiv of $ClTi(OCHMe_2)_3$. It is possible that at higher concentrations these titanium enolates form aggregates, which could be less selective, but nothing is known about the degree of aggregation of titanium enolates, and determination at −78 °C will be needed since aggregation is probably more likely at lower temperatures. Moreover, it is actually only the aggregation state of the transition structure and not that of the enolate that directly determines the selectivity (Curtin–Hammett principle[33,34]).

A limitation of the model shown in Scheme I is that the $Ti(OCHMe_2)_4$ diastereofacial selectivities and reactivities are not identical with those from $ClTi(OCHMe_2)_3$. For this model, since both titanium reagents result in the same enolate **8**, selectivities with an excess of either reagent should be exactly the same. In fact, only with benzaldehyde is the selectivity ratio the same within experimental error for both reagents, while with both isobutyraldehyde and propionaldehyde the selectivity ratios are significantly lower for $Ti(OCHMe_2)_4$ than for $ClTi(OCHMe_2)_3$, even at concentrations of 0.04 M with 4 and 5 equiv, respectively, of $Ti(OCHMe_2)_4$. The unreactivity of pivalaldehyde in the presence of $Ti(OCHMe_2)_4$ under these conditions also indicates that the $Ti(OCHMe_2)_4$- and $ClTi(OCHMe_2)_3$-mediated aldol reactions are not occurring through exactly the same enolate. Perhaps the simplest explanation of this low reactivity of pivalaldehyde with $Ti(OCHMe_2)_4$, even though it reacts normally with $ClTi(OCHMe_2)_3$, is that through ligand exchange the reactive enolate in the latter case has a *chloro* ligand on titanium [C=COTi(Cl)$(OCHMe_2)_2$], making it a stronger Lewis acid, and is not the triisopropoxy species **8** necessarily present with the $Ti(OCHMe_2)_4$ reagent. The major reaction path could be via a transition structure having a *chloro* ligand even if the *chloro* enolate were present in lesser concentration, but were more reactive, than **8**

(35) Heathcock, C. H. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: Oxford, 1983; pp 27–43.

(36) If the $k_1$ route were the source of the lowered selectivity near 1 equiv of Ti, the simple mass law effect would lower the concentration of lithium enolate **6** as excess Ti reagent were added, but because **6** must be present in very low concentration (since, as discussed four paragraphs above, the rate of the reaction is much slower in the presence of Ti), the change in concentration of **6** must be rather gradual over the range 1–2 equiv of Ti. Consequently, the contribution of **6** to the product ratio **2**:**3** must change gradually. A more abrupt change would result if **6** were aggregated under these conditions but the titanium enolate **8** were monomeric or less aggregated than **6**, yet even tetrameric Li species and monomeric **8** should give a too gradual change of **2**:**3**. Also, the fact that the change of selectivity occurs near 2 equiv of titanium would then be simply a coincidence based on the values of $k_1$, $k_3$, $K_1$, and $K_2$. However, if the $k_2$ route were the source of the lowered selectivity near 1 equiv of Ti, the change in selectivity should be abrupt in the present case as long as $K_2 \gg 1$. Because the titanium reagent $ClTi(OCHMe_2)_3$ would be a stronger Lewis acid than **8** (since **8** has four oxygen ligands on Ti), $K_2 \gg 1$ and, as a result, addition of excess $ClTi(OCHMe_2)_3$ would convert an equivalent amount of **7** into **8**. Consequently, at 2 equiv of Ti, essentially all of **7** would have been converted into **8**. A small amount of quenching of the enolate or simplifications inherent in this model could account for the fact that the abrupt change in stereoselectivity occurs at 1.75 equiv instead of 2.0. For example, if quenching were ≈12.5%, then the actual amount of enolate species present would be 0.875 equiv, and this would be converted almost entirely into **8** when the Ti added amounted to twice as much, i.e., 2 × 0.875 = 1.75 equiv. Because of this deviation from the value of 2.0 and because we have data for only one aldehyde so far, we feel that the ate complex **7** is not yet proven to be the mechanistic source of the reduced selectivities observed near 1 equiv of Ti.

(Curtin–Hammett principle[33,34]). This observation on pivaldehyde is the first indication of possible direct mechanistic involvement of such a monochloro enolate species; there is no other experimental evidence or literature precedent. We plan further experimental tests of this hypothesis. It raises the very interesting questions of whether all of the reactions mediated by $ClTi(OCHMe_2)_3$ proceed through transition structures bearing a chloro ligand on titanium and whether mixed-ligand enolate complexes may have novel and useful properties. An understanding of this phenomenon would be desirable as an aid in designing further reactions, including potential chelation-controlled aldol reactions.

Though the model presented here is the simplest consistent with the data, it does require various assumptions to make it so. Consequently, it is conceivable that future experimental results could implicate a more complex model involving aggregated titanium species. We are exploring the possibility of such aggregation, which, if present, may have interesting mechanistic consequences as well as important and useful applications.

## Conclusions

Several main conclusions can be drawn from this work. We have shown that titanium-mediated aldol reactions of chiral ketone **1** conveniently give very high diastereofacial selectivities, and we have determined the conditions for optimum control of these reactions. Their low cost and low toxicity, as well as ease of handling, should make titanium enolates especially useful to synthetic chemists. We have discovered a previously unreported effect of an excess of titanium reagent used to generate these enolates. Some of the previous work on titanium enolates in aldol reactions should be reconsidered in light of these results. We have observed a surprising similarity between $Ti(OCHMe_2)_4$- and $ClTi(OCHMe_2)_3$-mediated aldol reactions. $Ti(OCHMe_2)_4$ is a very inexpensive and easily handled reagent, and this appears to be the first report of its use in diastereofacially selective aldol reactions. Our results set the stage for future work to further explain and determine the usefulness of $Ti(OCHMe_2)_4$ as a substitute for $ClTi(OCHMe_2)_3$ in other aldol reactions.

## Experimental Section

**Materials and Methods.** Reagents and solvents were dried and/or purified before use.[37] Diisopropylamine and pyridine were distilled from $CaH_2$. THF and diethyl ether were distilled from sodium metal–benzophenone ketyl immediately prior to use. $ClTi(OCHMe_2)_3$ and $Ti(OCHMe_2)_4$ were distilled under reduced pressure. Benzaldehyde was dried with anhydrous sodium carbonate, filtered, and distilled under reduced pressure from zinc dust. Propionaldehyde, isobutyraldehyde, and trimethylacetaldehyde were dried with $CaSO_4$, filtered, and distilled immediately prior to use. All reactions and distillations were conducted under argon with oven-dried glassware (160 °C) that was flame-dried under a stream of argon.

Solvent systems are described as volume:volume ratios before mixing. Baker or Whatman silica gel (40-μm average particle size) was used for flash chromatography. Baker glass-backed TLC plates (with fluorescence) were used for analysis of reactions and fractions.

Melting points were determined on a Thomas–Hoover melting point apparatus and are reported uncorrected. Infrared spectra were recorded on a Perkin-Elmer 735 infrared spectrometer and calibrated with the 1601-$cm^{-1}$ resonance of polystyrene. Abbreviations accompanying IR frequencies are defined as follows: br = broad, s = strong. $^1H$ NMR spectra were recorded at 200 MHz on an IBM WP-200 spectrometer, at 250 MHz on a Bruker WM-250 or AF-250 spectrometer, or at 500 MHz on a Bruker AM-500 spectrometer. $^{19}F$ NMR spectra were recorded at 188.2 MHz on the IBM WP-200 spectrometer. $^{13}C$ NMR spectra were recorded at 50.3 MHz on the IBM WP-200 spectrometer or at 125.8 MHz on the Bruker AM-500 spectrometer with complete proton decoupling. All NMR spectra are reported in ppm on the δ scale relative to internal tetramethylsilane for $^1H$ and $^{13}C$ NMR. The $^{19}F$ NMR data are also reported in ppm, relative to external ethyl trifluoroacetate. NMR data are presented in the following manner: chemical shift (δ), (multiplicity (abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, dq = doublet of quartets, br = broad peak), coupling constant in hertz, integration, and assignment).

High-resolution mass spectra (CI = chemical ionization) were obtained from the University of Pennsylvania Mass Spectrometry Facility of the Chemistry Department. Single-crystal X-ray structure determination was performed by Dr. P. Carroll of the University of Pennsylvania X-ray Crystallography Facility of the Chemistry Department with an Enraf-Nonius CAD-4 automatic diffractometer.

Flash chromatography was carried out using the procedure of Still et al.[38] Eluent compositions follow each column description. Fractions were analyzed by TLC with visualization by either fluorescence or staining with 2.3% ethanolic phosphomolybdic acid.

Rotary evaporation refers to removal of volatile components, including solvent, under water aspirator pressure on a Büchi Rotavapor Evaporator at ≤30 °C.

**Synthesis of (*S*)-(−)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-cyclohexylbutan-2-one (1).** This chiral ketone was prepared from (*S*)-(+)-mandelic acid according to the literature procedure.[39]

**General Procedure for Formation and Reaction of Lithium Enolate of (*S*)-(−)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-cyclohexylbutan-2-one (1).** The procedure followed is similar to that developed by Heathcock et al.[40] Reactions were run in a septum-capped, 25-mL, flame-dried flask under argon. All reagents were added via oven-dried hypodermic syringes. To 1.2 equiv (based on ketone **1**) of diisopropylamine in THF (0.17 M based on ketone **1**) at 0 °C (ice bath) was added 1.1 equiv of an *n*-butyllithium solution in hexanes. After it was stirred for 15 min, the solution was cooled to −78 °C (dry ice/acetone bath), 1.0 equiv of (*S*)-(−)-1-[(*tert*-butyldimethylsilyl)oxy]-1-cyclohexylbutan-2-one (**1**) was added dropwise over 2 min (added neat using a weighed syringe), and the reaction was stirred for 1.5 h at −78 °C. The aldehyde (2.0 equiv) was added, and the reaction was quenched after 15 min with the addition of a saturated $NH_4Cl$ solution. After warming to ca. 25 °C, the mixture was extracted with diethyl ether three times. The organic layer was dried with $Na_2SO_4$, vacuum filtered, concentrated by rotary evaporation, and placed under high vacuum (ca. 0.05 mmHg) for at least 2 h.

**General Procedure for Formation and Reaction of Titanium Enolates of (*S*)-(−)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-cyclohexylbutan-2-one (1).** The reactions described below were run on 0.5–2.5-mmol scale. The procedure is similar to that of Reetz et al.[41] with some modifications.

The lithium enolate was first generated as described above at various concentrations (specific molarity is given for each case). At −78 °C, 1–3 equiv (based on amount of LDA, specific amount given with each example) of either $ClTi(OCHMe_2)_3$ or $Ti(OCHMe_2)_4$ (neat) was added dropwise with stirring. The solution immediately turned to a clear, light to dark yellow. It was allowed to warm to −30 °C over 1 h and then kept between −30 and −40 °C for 0.5 h. After the solution was cooled to −78

**Table III.** X-ray Crystal Data[a]

| compd | 9 | 10 |
|---|---|---|
| formula | $C_{30}H_{41}SiNO_6$ | $C_{15}H_{28}O_3$ |
| formula wt | 539.75 | 256.39 |
| cryst class | monoclinic | orthorhombic |
| space gp | $P2_1$; $Z = 4$ | $P2_12_12_1$; $Z = 4$ |
| cell constants | | |
| $a$, Å | 6.330 (1) | 6.329 (1) |
| $b$, Å | 29.580 (1) | 10.155 (1) |
| $c$, Å | 16.515 (1) | 24.076 (1) |
| $\beta$, deg | 91.87 (1) | |
| $\mu$, $cm^{-1}$ | 1.10 | 0.70 |
| $D$(calc), $g/cm^3$ | 1.160 | 1.100 |
| $\theta$ range, deg | 2–25 | 2–27.5 |
| no. of reflcns measd | 6105 | 2083 |
| no. of reflcns used in refinement | 2659 ($I > 3\sigma$) | 882 ($I > 3\sigma$) |
| $R_1$ | 0.060 | 0.053 |
| $R_2$ | 0.074 | 0.065 |

[a] The reflections were measured with an automatic four-circle diffractometer equipped with Mo Kα radiation (0.71073 Å). The structure was solved with a multisolution tangent formular approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.

(37) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: Oxford, 1980.

(38) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(39) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47–63.

(40) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290–2300.

(41) Reetz, M. T.; Steinbach, R.; Kesseler, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 864–865; *Angew. Chem. Suppl.* **1982**, 1899–1905.

°C, 2.0 equiv of the aldehyde was added. The mixture was allowed to warm again to −40 °C over 1.5 h and then kept between −40 and −50 °C for 1.5–2 h. The reaction was quenched with the addition of a saturated solution of $NH_4F$. After it was warmed to ca. 25 °C, the mixture was extracted with diethyl ether three times. The organic layers were washed with saturated NaCl and dried with sodium sulfate. The solvent was removed by rotary evaporation, and the crude oil was placed on a vacuum pump (ca. 0.05 mmHg) for at least 2 h.

**(1*S*,3*R*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-cyclohexyl-4-hydroxy-3-methyl-4-phenylbutan-2-one (2a).** The aldol condensation was carried out with **1** (151 mg, 0.531 mmol) and benzaldehyde according to the general procedure for titanium-mediated aldol reactions above, at a concentration of ca. 0.17 M using 3.0 equiv of $ClTi(OCHMe_2)_3$. The ratio of diastereomers was determined by $^1H$ NMR analysis, using multiple scans (approximately 1000) with a relaxation delay of 5.0 s, on the crude product mixture. $^1H$ NMR (250 MHz, $CDCl_3$, carbinol protons, $C_4H$): (**2a**) δ 5.05 (d, $J$ = 3.2); (**3a**) δ 4.92 (d, $J$ = 3.6). The ratio of **2a** to **3a** was 76:1 ± 2.6. The reaction was carried out three times, and the ratio reported is an average with standard deviation. Purification of the crude mixture was achieved by flash chromatography (9:1, hexanes–ethyl acetate, $R_f$ = 0.28) and yielded 177 mg (85%) of a colorless oil, **2a**. IR (neat): 3500 (br), 3100, 3060, 2950, 2875, 1720 (s), 1615, 1455, 1255, 1000, 840 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): δ 7.3–7.2 (m, 5 H, $C_6H_5$), 5.05 (dd, $J$ = 3.2, 1.3 (collapses to d in $CDCl_3/D_2O$, $J$ = 3.2), 1 H, C*H*OH), 3.92 (d, $J$ = 5.0, 1 H, C*H*OSi), 3.50 (br s, $D_2O$ exchangeable, 1 H, O*H*), 3.18 (dq, $J$ = 3.2, 7.2, 1 H, C*H*Me), 1.8–0.8 (m, 11 H, cyclohexyl), 1.0 (d, $J$ = 7.2, 3 H, $CH_3CH$), 0.92 (s, 9 H, $(CH_3)_3C$), 0.04 and 0.03 (2s, 3 H each, 2 $CH_3Si$). $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 217.8 (*C*=O), 141.6, 128.2, 127.2, 125.9 ($C_6H_5$), 82.6 (*C*OSi), 72.6 (*C*OH), 46.9, 41.6, 29.9, 27.4, 26.3, 26.1, 25.8, 18.2, 10.4 (4 $CH_3C$, *C*HMe, $Me_3CSi$, cyclohexyl; 3 equiv), −4.4, −5.0 (2 $CH_3Si$).

CI MS: $m/e$ 391.2672 $(M + H)^+$. Calcd for $C_{23}H_{39}O_3Si$: $m/e$ 391.2668.

**(1*S*,3*R*,4*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-cyclohexyl-4-hydroxy-3-methylhexan-2-one (2b).** Enolization of silyloxy ketone **1** (173 mg, 0.609 mmol), condensation with propionaldehyde and workup were carried out according to the general titanium aldol procedure at a concentration of 0.083 M, using 4.0 equiv of $ClTi(OCHMe_2)_3$. The ratio of diastereomers was determined by preparing their trifluoroacetate esters[19] and integration of the $^{19}F$ NMR. The reaction was done twice, and the ratio is reported as an average with average deviation. $^{19}F$ NMR (188.2 MHz, $CDCl_3$, $CF_3$ fluorines); ($CF_3CO_2Et$, −76.28 ppm): δ (**2b**) −75.8 (s); (**3b**) −75.7 (s). These δ values are slightly concentration dependent, but the difference between **2b** and **3b** is always constant. The ratio of **2b** to **3b** was 114:1 ± 11. The crude aldol products were purified by flash chromatography (9:1, hexanes–ethyl acetate, $R_f$ = 0.24) and yielded 142 mg (88%) of a colorless oil, **2b**. IR (neat): 3560 (br), 2970 (s), 2880, 1710, 1455, 1255, 840 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): δ 3.84 (d, $J$ = 5.4, 1 H, C*H*OSi), 3.71 (m, (collapses to ddd in $CDCl_3/D_2O$, $J$ = 7.9, 5.6, 2.0), 1 H, C*H*OH), 3.20 (br s, $D_2O$ exchangeable, 1 H, O*H*), 2.98 (dq, $J$ = 2.0, 7.2, 1 H, C*H*Me), 1.8–0.8 (m, 16 H, cyclohexyl and $CH_3CH_2$), 1.05 (d, $J$ = 7.2, 3 H, $CH_3CH$), 0.9 (s, 9 H, $(CH_3)_3C$), 0.01 and −0.01 (2s, 3 H each, 2 $CH_3Si$). $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 218.7 (*C*=O), 82.8 (*C*OSi), 72.2 (*C*OH), 43.2, 41.8, 29.7, 27.48, 26.6, 26.2, 26.1, 25.8, 25.7, 18.1, 10.4, 9.6 (5 $CH_3C$, *C*HMe, $CH_3CH_2$, $(Me)_3CSi$, cyclohexyl; 2 equiv), −4.6, −5.0 (2 $CH_3Si$).

CI MS: $m/e$ 343.2641 $(M + H)^+$. Calcd for $C_{19}H_{39}O_3Si$: $m/e$ 343.2668.

**(1*S*,3*R*,4*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-cyclohexyl-4-hydroxy-3,5-dimethylhexan-2-one (2c).** Enolization of silyloxy ketone **1** (173 mg, 0.609 mmol), condensation with isobutyraldehyde, and workup were carried out according to the general titanium aldol procedure at a concentration of 0.083 M, using 3.0 equiv of $ClTi(OCHMe_2)_3$. The ratio of diastereomers was determined by preparing their trifluoroacetate esters[19] and integration of the $^{19}F$ NMR. The reaction was done three times, and the ratio is reported as an average with standard deviation. $^{19}F$ NMR (188.2 MHz, $CDCl_3$, $CF_3$ fluorines); ($CF_3CO_2Et$, −76.28 ppm): δ (**2c**) −76.0 (s); (**3c**) δ −75.9 (s). The ratio of **2c** to **3c** was 138:1 ± 1.0. The crude aldol products were purified by flash chromatography (9:1, hexanes–ethyl acetate, $R_f$ = 0.39) and yielded 172 mg (79%) of a colorless oil, **2c**, which freezes in the refrigerator to give a colorless solid (mp < 20 °C). IR (neat): 3560 (br), 2960 (s), 2880, 1720, 1460, 1265, 850 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3/D_2O$): δ 3.85 (d, $J$ = 5.5, 1 H, C*H*OSi), 3.35 (dd, $J$ = 9.1, 1.7, 1 H, C*H*OH), 3.15 (dq, $J$ = 1.7, 7.2, 1 H, C*H*Me), 1.8–0.8 (m, 12 H, cyclohexyl and $Me_2CH$), 1.05 (d, $J$ = 7.1, 3 H, $CH_3CHC{=}O$), 1.0 (d, $J$ = 6.8, 3 H, $CH_3{}^aCHCH_3$), 0.91 (s, 9 H, $(CH_3)_3C$), 0.82 (d, $J$ = 6.5, 3 H, $CH_3{}^bCHCH_3$), 0.01 and −0.03 (2s, 3 H each, 2 $CH_3Si$). $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 219.0 (*C*=O), 82.9 (*C*OSi), 76.1 (*C*OH), 41.9, 41.3, 30.3, 29.7, 27.9, 26.2, 26.1, 25.8, 25.82, 19.7, 18.8, 18.2, 9.3 (6 $CH_3C$, *C*HMeC=O, $Me_2CH$, $Me_3CSi$, cyclohexyl; 2 equiv), −4.5, −5.0 (2 $CH_3Si$).

CI MS: $m/e$ 357.2843 $(M + H)^+$. Calcd for $C_{20}H_{41}O_3Si$: $m/e$ 357.2825.

**(1*S*,3*R*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-cyclohexyl-4-hydroxy-3,5,5-trimethylhexan-2-one (2d).** The aldol condensation was carried out with **1** (151 mg, 0.554 mmol) and pivalaldehyde according to the general procedure for titanium-mediated aldol reactions, except that the condensation was run at 10 °C higher temperature (−40 to −30 °C), at a concentration of 0.11 M using 3.0 equiv of $ClTi(OCHMe_2)_3$. The ratio of diastereomers was determined by $^1H$ NMR analysis, using multiple scans (approximately 1000) with a relaxation delay of 5.0 s, on the crude product mixture. $^1H$ NMR (250 MHz, $CDCl_3$, $C_1H$): (**2d**) δ 3.95 (d, $J$ = 4.5); (**3d**) δ 3.84 (d, $J$ = 5.0). The ratio of **2d** to **3d** was ≥117:1. The reaction was carried out twice. Purification of the crude mixture was achieved by flash chromatography (9.5:0.5 hexanes–ethyl acetate, $R_f$ = 0.26) and yielded 154 mg (75%) of a colorless oil, **2d**. IR (neat): 3565 (br), 2955 (s), 2875, 1720, 1475, 1265, 845, 785 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3/D_2O$): δ 3.95 (d, $J$ = 4.5, 1 H, C*H*OSi), 3.43 (d, $J$ = 1.0, 1 H, C*H*OH), 3.16 (dq, $J$ = 1.0, 7.1, 1 H, C*H*Me), 1.8–0.8 (m, 11 H, cyclohexyl), 1.11 (d, $J$ = 7.1, 3 H, $CH_3CH$), 0.91 and 0.94 (2s, 9 H each, 2 $(CH_3)_3C$), 0.05 and −0.04 (2s, 3 H each, 2 $CH_3Si$). $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 217.8 (*C*=O), 82.2 (*C*OSi), 76.6 (*C*OH), 41.9, 41.2, 35.4, 30.1, 27.5, 27.1, 26.4, 26.2, 26.0, 25.9, 11.2 (7 $CH_3C$, *C*HMe, $Me_3CC$, cyclohexyl; 4 equiv), 18.3 ($Me_3CSi$), −4.4 and −5.0 (2 $CH_3Si$).

CI MS: $m/e$ 371.2994 $(M + H)^+$. Calcd for $C_{21}H_{43}O_3Si$: $m/e$ 371.2981.

**(1*S*,3*R*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-cyclohexyl-3-methyl-4-[(4′-nitrobenzoyl)oxy]-4-phenylbutan-2-one (9).** To 329 mg (0.842 mmol) of the hydroxy silyloxy ketone **2a** was added 160 mg (0.82 mmol) of 4-nitrobenzoyl chloride, 100 mg of 4-(dimethylamino)pyridine, and 8 mL of pyridine under argon. The reaction mixture was stirred at ca. 25 °C for 12 h and then poured onto a cold mixture of diethyl ether (50 mL) and 1 M HCl (50 mL). The layers were separated, and the aqueous layer was extracted once with ether (25 mL). The combined organic layers were washed with 1 M HCl and then with dilute $Na_2CO_3$. After drying and removal of the solvent, the crude product was placed under vacuum (ca. 0.05 mmHg) for 4 h. Recrystallization from hexane yielded 131 mg (29%) of a white solid, **9**. Mp: 100–101 °C. IR (KBr): 3060, 2950, 2880, 1730 (s), 1620, 1530, 1460, 1355, 1275, 1110, 960, 840 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): δ 8.26 (m, 4 H, 4′-$NO_2C_6H_4$), 7.4–7.2 (m, 5 H, $C_6H_5$), 6.34 (d, $J$ = 8.1, 1 H, $CHO_2CC_6H_4NO_2$), 4.00 (d, $J$ = 2.9, 1 H, C*H*OSi), 3.54 (m, 1 H, C*H*Me), 1.7–0.6 (m, 11 H, cyclohexyl), 1.29 (d, $J$ = 7.0, 3 H, $CH_3CH$), 0.93 (s, 9 H, $(CH_3)_3C$), 0.02 and 0.01 (2s, 3 H each, 2 $CH_3Si$). $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 211.0 ($C_2C{=}O$), 163.5 ($OC{=}O$), 150.6, 138.7, 135.7, 130.7, 128.5, 128.3, 127.0, 123.6 ($C_6H_5$, 4′-$NO_2C_6H_4$, 4 equiv), 81.7 (*C*OSi), 76.7 ($CHO_2C$-$C_6H_4NO_2$), 47.9, 41.3, 30.2, 26.5, 26.1, 26.0, 25.9, 25.8, 18.3, 14.0 (4 $CH_3C$, *C*HMe, $Me_3CSi$, cyclohexyl; 2 equiv), −4.4 and −5.0 (2 $CH_3Si$).

For X-ray analysis, crystals were grown from 9:1 hexanes–diethyl ether at ca. 25 °C. X-ray data are given in Table III and the supplementary material.

CI MS: $m/e$ 557.2995 $(M + NH_4)^+$. Calcd for $C_{30}H_{45}N_2O_6Si$: $m/e$ 557.3047.

**(1*S*,3*R*,4*R*)-1-Cyclohexyl-1,4-dihydroxy-3,5,5-trimethylhexan-2-one (10).** To 593 mg (1.6 mmol) of the hydroxy silyloxy ketone **2d** in 10 mL of $CH_3CN$ was added 0.5 mL of concentrated HF. The reaction was stirred at ca. 25 °C for 4 h and worked up by pouring onto a mixture of 50 mL of diethyl ether and 50 mL of water. The layers were separated, and the aqueous layer was extracted with 25 mL of diethyl ether. The organic layer was washed with dilute sodium bicarbonate and dried ($Na_2SO_4$) to give after solvent removal an off-white solid. Recrystallization from petroleum ether (bp 40–60 °C) yielded 116 mg (76%) of a pure white solid, **10**. Mp: 73.5–74.5 °C. IR (KBr): 3530, 3440, 2950 (s), 2885, 1705, 1465, 1250, 1150, 995 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): δ 4.23 (dd, $J$ = 5.8, 2.4, 1 H, O=CC*H*OH), 3.54 (dd, $J$ = 3.0, 0.8, 1 H, $(CH_3)_3CCHOH$), 3.24 (d, $J$ = 5.7, 1 H, O=CCHO*H*), 3.09 (dq, $J$ = 0.8, 7.2, 1 H, C*H*Me), 2.63 (d, $J$ = 3.0, 1 H, $(CH_3)_3CCHOH$), 1.9–0.9 (m, 11 H, cyclohexyl), 1.18 (d, $J$ = 7.2, 3 H, $CHCH_3$), 0.97 (s, 9 H, $(CH_3)_3C$). $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 217.9 (*C*=O), 78.9, 76.6 (2 *C*HOH), 41.6, 41.5, 35.4, 30.2, 26.8, 26.5, 25.9, 25.8, 25.7, 11.9 (4 $CH_3C$, *C*HMe, $Me_3C$, cyclohexyl; 2 equiv).

Crystals for X-ray analysis were grown from 9:1 hexanes–diethyl ether at ca. 25 °C. X-ray data are given in Table III and the supplementary material.

CI MS: $m/e$ 257.2136 $(M + H)^+$. Calcd for $C_{15}H_{29}O_3$: $m/e$ 257.2117.

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**Supplementary Material Available:** Tables of refined atomic positional and thermal parameters for the two X-ray structures reported (6 pages). Ordering information is given on any current masthead page.

# 11 K Charge Density Study of 2,5-Diaza-1,6-dioxa-6a-thiapentalene Containing a Short Nonbonded S···O Contact

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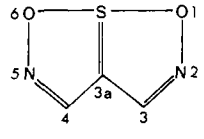
**Abstract:** In the compound 2,5-diaza-1,6-dioxa-6a-thiapentalene, the S···O distance is 1.83 Å, which is intermediate between a covalent bond length and the sum of the atomic van der Waals radii. The charge density distribution in the molecule was not clearly understood from previous 122 K X-ray and neutron measurements. In the present study, results obtained with 11 K X-ray diffraction measurements and aspherical atom refinement using the program MOLLY are presented. The static deformation model maps are in good agreement with the theoretical maps obtained from a previous local density functional calculation. The mechanism proposed to interpret the X–S···O interaction depends on the electronegativity of X and involves a $\sigma$-type coupling between oxygen and sulfur p orbitals. Furthermore, the molecule is stabilized through sulfur d orbitals. The experimental charge distribution obtained at 11 K supports this theory. The 11 K study is more conclusive than the previous 122 K study, which used a spherical treatment of the electron density distribution. It leads to the rejection of the controversial deduction that oxygen is in a spherical state with little hybridization. A reinvestigation of the previous 122 K X-ray data using the MOLLY program is qualitatively consistent with these results, although strongly influenced by the thermal effects.

Many compounds containing the X–S···O configuration (X = O, C) exhibit very short X···O contacts.[1a,b] The S···O distance varies between 1.83 and 2.96 Å. This is longer than the covalent S–O bond length of 1.56–1.65 Å[1b] yet much shorter than the sum of the van der Waals radii, which is 3.3 Å.[2] In previous studies by X-ray and neutron diffraction on compounds with S···O contacts of 2.24 and 2.68 Å,[3a,b,4] the X–N deformation electron density maps showed only weak features in the sulfur–oxygen region. This finding was not concordant with theoretical analysis,[3b,5] which showed that in these compounds the X–S···O attraction is mainly due to interactions between p nonbonded orbitals of the oxygen atom and p and d orbitals of sulfur.

In thiapentalene derivatives where X = O the molecules are planar and show a symmetrical conjugated structure;[1a] the system O···S···O is symmetric, and the S···O distance is about 1.85 Å.

In order to gain insight in the molecular stabilization in these compounds, we have undertaken an investigation of the charge density in 2,5-diaza-1,6-dioxa-6a-thiapentalene (I). In a previous




I

work,[4] we obtained experimental deformation electron density from a refinement of combined 122 K X-ray and neutron diffraction data using a radial deformation model. Electron density deformation maps showed a very diffuse O···S···O region, and little positive density was observed in the lone-pair region of the oxygen atoms. This was in contradiction to the theoretical maps obtained by a local density function calculation.[5]

A multipole refinement using also combined 122 K X-ray and neutron diffraction data led to controversial conclusions about the density in the region around sulfur and oxygen.[5]

In order to clarify this point, we undertook an X-ray diffraction study at 11 K on I.

## Experimental Section

Crystals of 2,5-diaza-1,6-dioxa-6a-thiapentalene were grown from cyclohexane solution. The crystal used for data collection was bounded by nine well-developed faces and had a volume of 0.0091 mm$^3$ with the longest dimension 0.3 mm. It was mounted in a thin-walled capillary to prevent sublimation.

Data were collected at 11 ± 1 K using Nb-filtered Mo K$\alpha$ radiation ($\lambda$ = 0.7107 Å). The crystal was cooled in a two-stage closed-cycle helium cryostat, a modified DISPLEX CS201 (manufactured by Air Products and Chemicals, Inc., and now by Intermagnetics General Corp.) mounted on a HUBER diffractometer.[6] Low-temperature unit cell dimensions were checked several times during the data collection period,

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