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Communication

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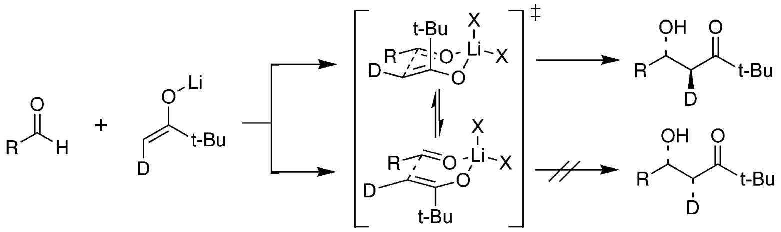

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Experimental Evidence for Chair-Like Transition States in Aldol Reactions of Methyl Ketone Lithium Enolates: Stereoselective Synthesis and Utilization of a Deuterium-Labeled Enolate as a Probe of Reaction Stereochemistry

Christopher M. Liu, William J. Smith, III, Darin J. Gustin, and William R. Roush*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1055

Received February 4, 2005; E-mail: roush@umich.edu

The aldol reaction is an important transformation in organic synthesis.[1] The stereochemistry of aldol reactions of ethyl ketone metal enolates is typically rationalized by invoking chairlike Zimmerman−Traxler transition states.[2] The factors that govern the diastereofacial selectivity of aldol reactions involving chiral aldehyde coupling partners are increasingly well appreciated.[3−5] However, factors that control the diastereofacial selectivity of reactions of methyl ketone enolates and chiral aldehyde partners remain poorly understood. While analysis of product distributions of methyl ketone aldol reactions suggest competition occurs between chairlike and boatlike transition states,[6−8] definitive experimental evidence in support of this hypothesis is lacking.

Several years ago our laboratory demonstrated that the aldol reactions of chiral aldehydes **1**−**4** with methyl ketone partners are strongly influenced by the nature of the metal enolate, the C(3)−O-protecting group, and the 2,3-stereochemistry of the aldehyde substrate.[8] By judicious control of these three variables, either the Felkin (**5**) or anti-Felkin (**6**) aldol products could be obtained with excellent selectivity (Figure 1). These results were rationalized by invoking a chairlike transition state (analogous to that of **7a**) leading to the Felkin adduct **5**, and a boatlike transition state (t.s.) (analogous to that of **9a**) for formation of the anti-Felkin aldol **6**.[8] However, this analysis was not entirely satisfying, since reasonable chairlike and boatlike transition states can be invoked for formation of both products (Figure 2).

It was readily apparent that all four of the competing chairlike and boatlike transition states (**7**−**10**) can be distinguished if the enolate contains a deuterium substituent (Figure 2). Accordingly, we have developed and report herein a stereoselective synthesis of deuterium-labeled enol silane **18**-(*E*) and studies of aldol reactions of the derived lithium enolate.[9,10] Our results demonstrate chairlike transition states **7** and **10** are highly favored for reactions with both achiral and chiral aldehyde reaction partners.[11]

Deuterium-labeled enol silane **18** was synthesized via a four-step procedure starting from norbornadiene (Scheme 1). Deuterioboration[12,13] of **15** (NaBD$_4$, BF$_3$·OEt$_2$, THF, −78 °C) proceeded with 9:1 selectivity; the diastereomerically pure, d^1-exo alcohol **16** was isolated in 68% yield by chromatography. Oxidation of **16** and then addition of *t*-BuLi and protection of the resulting tertiary alcohol as a TMS ether provided **17** ($\geq$97% d^1-exo) in 72% overall yield. Flash vacuum pyrolysis of **17** at 380 °C and 2 mmHg then provided an inseparable mixture of enol silanes d^1-**18**-(*E*), d^1-**18**-(*Z*), and d^0-**18** in 79% yield. The Z(O) enol silane d^1-**18**-(*Z*) and diprotio enol silane d^0-**18** each typically constituted 4−7% of the mixture (^{1}H NMR analysis). NMR studies of enol silane d^1-**18**-(E) were performed in C_6D_6 to avoid olefin isomerization that occurred during exposure to $CDCl_3$.

Treatment of enol silane **18** (mixture as described above) with MeLi in THF at 0 °C followed by warming to 23 °C generated a solution of the corresponding lithium enolate,[9,10] which was then cooled to −78 °C. The aldehyde was then added as a concentrated solution in THF, and the reaction was quenched by addition of aqueous NH$_4$Cl after 30 s. The ratios of diastereomeric aldol products were then determined by ^{1}H NMR analysis of the crude product mixture. The stereochemistry of **19a** was confirmed by stereoselective reduction to the 1,3-syn diol and conversion to the acetonide derivative (see Supporting Information). The stereochemistry of **11a**−**d** and **14a**−**d** were assigned by application of our NMR method for stereochemical assignment of β-hydroxyl ketones.[14]

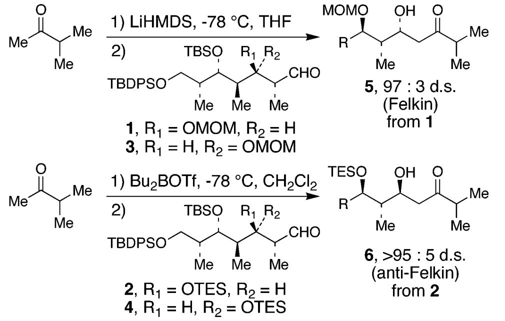

Figure 1. Divergent Felkin versus anti-Felkin selectivity in the aldol reactions of chiral aldehydes **1** and **2**.

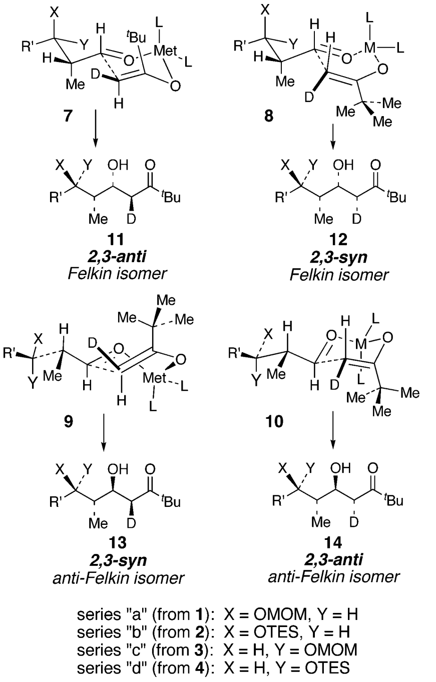

Figure 2. Chairlike and boatlike transition states for aldol reactions of chiral aldehydes **1**−**4** and the deuterium-labeled lithium enolate derived from enol silane **18**.

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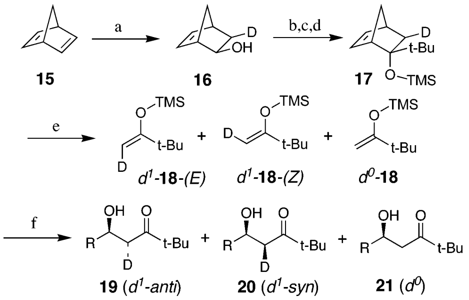
Table 1. Results of the Aldol Reaction of Chiral and Achiral Aldehdyes with a Deuterium-Labeled Enol Silane

entry	aldehyde	yield (%)	products	ds	enol silane isomeric purity[a] d^1-**18**(E):d^1-**18**(Z):d^0-**18**	major aldol product isomeric purity[a] (cf., 19:20:21)	minor aldol product isomeric purity[a] (cf., 19:20:21)
1	PhCHO	58	**19a**, R = Ph	–	89:6:5	88:6:6[b]	–
2	*i*-PrCHO	83	**19b**, R = *i*-Pr	–	86:6:8	87:6:7	–
3	*t*-BuCHO	73	**19c**, R = *t*-Bu	–	86:6:8	82:8:10	–
4	**1**	77	**11a**: **14a**	95:5	89:6:5	(**11a**) 91:5:4	(**14a**) maj:min:ND
5	**2**	77	**11b**: **14b**	60:40	89:5:6	(**11b**) 88:7:5	(**14b**) 82:10:5
6	**3**	89	**11c**: **14c**	7:93	85:10:5	(**14c**) 81:11:8	(**11c**) 74:18:8
7	**4**	93	**11d**: **14d**	13:87	87:6:7	(**14d**) 72:20:8	(**11d**) 81:12:7

[a] Isomeric purity determined by NMR analysis (±2%); [b] Isomer ratio determined following reduction to the syn-1,3 diol and conversion to the acetonide derivative (see Supporting Information).

Scheme 1. Synthesis and Aldol Reactions of Deuterium-Labeled Enol Silane **18**[a]



[a] Reactions and conditions: (a) $NaBD_4$, $BF_3{\cdot}OEt_2$, THF, −78 °C → 23 °C; $NaBO_3{\cdot}H_2O$, 68%, 9:1 dr; (b) $(COCl)_2$, DMSO, NEt_3, 87%; (c) *t*-BuLi, −78 °C, 62%; (d) TMS-Cl, pyridine, 72%; (e) 380 °C, 2 mmHg, 79%; (f) MeLi, 0 °C → 23 °C; R−CHO, −78 °C, 53−93%.

The results presented in Table 1 show that, in the vast majority of cases, the isomeric purity of the enol silane **18** correlates well with the ratio and pattern of deuterium labeling in the aldol products. The results in entries 1−3 for aldol reactions with achiral aldehydes, indicate that the major aldol **19** has 2,3-anti stereochemistry, fully consistent with the involvement of a chairlike t.s. analogous to that of **7**. The aldol reactions of **18** and 2,3-anti aldehydes **1** and **2** (entries 4, 5) similarly exhibit excellent preservation of deuterium labeling in the major aldols **11a** and **11b**, respectively, again consistent with the chairlike t.s. **7a** (as previously predicted).[8] The pattern of deuterium labeling in the minor aldol **14b** deriving from **2** (entry 5) shows some erosion from the labeling pattern in **18**. Accordingly, it appears that **14b** derives predominately from chairlike t.s. **10b** (in contrast to our previous analysis)[8] with intervention of the competitive boatlike t.s. **9b**, with the **10b**:**9b** t.s. partition being ca. 10:1. Although the major and minor products of aldol reactions of the 2,3-syn aldehydes **3** and **4** (entries 6, 7) again are fully consistent with chairlike transition states **10c−d** (leading to major products **14c−d**) and **7c−d** (leading to minor products **11c−d)**, significant erosion of the deuterium-labeling patterns occurs especially in **11c** (entry 6) and **14d** (entry 7). In these cases, it is necessary to invoke the competing boatlike transition states **8c** and **9d**, respectively (ca. 5:1 chair to boat t.s. in each case), to rationalize the pattern of deuterium labeling in aldols **11c** and **14d**.[15]

In summary, we have demonstrated that the aldol reactions of methyl ketone lithium enolates proceed predominantly via chairlike transition states, with involvement of competitive boatlike transition states being implicated in only a limited number of cases. These results are consistent with predictions based on ab initio calculations of methyl ketone lithium enolate aldol reactions.[16,17] Attempts to extend this protocol to the examination of the transition states of aldol reactions of other methyl ketone metal enolates are in progress and will be reported in due course.

Acknowledgment. Support provided by the National Institutes of Health (GM 38436) is gratefully acknowledged.

Supporting Information Available: Complete experimental details and spectroscopic data for synthesis of **18** and all deuterium-labeled aldol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) A reviewer suggested that the stereochemical erosion seen in entries 6 and 7 might be due to (E)-to-(Z)-enolate isomerization during the aldol reaction. However, all aldol reactions were performed for 30 s or less, whereas enolate generation was performed over a period of ∼1 h at 0−23 °C (see SI for details). Therefore, if enolate instability were a problem, it should be reflected in 100% of the data entries in Table 1. Finally, identical product distribution and isotope-labeling patters were observed for experiments in which d^1-**18** was used as the limiting reagent (all data in Table 1 are for experiments in which d^1-**18** was used in excess).
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