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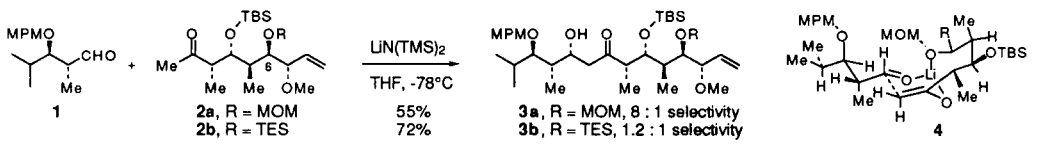
Diastereoselective Aldol Reactions of Chiral Aldehydes and Chiral Methyl Ketones: Dependence of Stereoselectivity on the Metal Enolate, the Aldehyde 2,3-Stereochemistry, and the Aldehyde β-Alkoxy Protecting Group

Darin J. Gustin, Michael S. VanNieuwenhze,[1] and William R. Roush*

Department of Chemistry, Indiana University, Bloomington, IN 47405

Abstract: The stereoselectivity of aldol reactions of chiral aldehydes ***5*** *and* ***11*** *with methyl ketone enolates is highly dependent on the aldehyde 2,3-stereochemistry, the aldehyde β-alkoxy protecting group, and the metal enolate. The selectivity trends are rationalized by a competition between chair-like and boat-like transition states.*

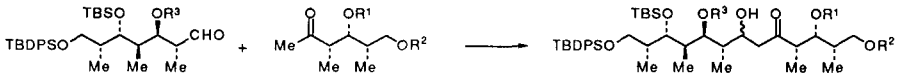
The aldol reaction is arguably one of the most important transformations in modern organic synthesis, as evidenced by its numerous applications to the synthesis of complex natural products.[2] The relationship between enolate geometry and product stereostructure is well established, and transition state models have been presented to rationalize the diastereofacial selectivity of aldol reactions of chiral aldehydes and chiral ketone enolates with achiral partners.[3,4] However, in spite of widespread investigations of this reaction and its many variants, the factors that determine the stereochemical outcome of aldol reactions involving chiral aldehydes and chiral ketones are not well understood.[5] For example, in recent work directed towards the synthesis of bafilomycin A_1, we showed that the stereochemical outcome of the aldol reaction of **1** and **2** is highly dependent on the protecting group at C(6) of **2** when lithium enolates were employed, but not when chlorotitanium enolates were used.[6] The results with the Li enolates were interpreted in terms of the chelated transition structure **4**. In order to gain further insight into the factors that control the stereochemical course of methyl ketone fragment assembly aldol reactions, we have studied the reactions of chiral aldehydes **5** and **11** with chiral methyl ketone **6** and isopropyl methyl ketone. We report herein our observation that the stereoselectivity of these reactions is remarkably dependent on the stereochemistry of the chiral aldehyde, the metal enolate, and especially the β-alkoxy protecting group of the 2,3-anti aldehydes **5**.



Aldehyde **5** and ketone **6**, which derive from intermediates in our approach to the C(3)-C(15) fragment of rutamycin B,[5a,c,7] are homochirally related to **1** and **2**. The only difference is that the C(5)-Me center is different in **6** compared to **2**. We therefore expected that the stereochemical course of the reactions of **5** and **6** would directly parallel **1** and **2** in the bafilomycin series. However, we quickly discovered that this was not the case, as indicated by the data summarized in Table 1 which show that the stereoselectivities of the lithium enolate aldol reactions are only modestly dependent on the protecting groups associated with the β and δ oxygen atoms (R^1 and R^2) of the ketone fragment (compare entries 1, 5 and 14 for reactions with **5a** and entries 8 and 15 for reactions with **5b**).[8,9]

The most striking feature of the data in Table 1 is that it is possible to prepare either aldol diastereomer ***7*** *or* ***8*** *with excellent selectivity simply by changing the enolate metal and the β alkoxy protecting group of* ***5*** *(R^3).* Thus, the aldol reaction of the lithium or titanium enolates of **6a** and aldehyde **5a** (R^3 = MOM) provides aldol **7** with 89 : 11 selectivity (entries 1-3), whereas the reaction of the enolborinate of **6a** or **6b** with aldehyde **5b** (R^3 = $SiEt_3$) provides the aldol **7** in the "anti-Felkin" series with ≤3 : 97 selectivity (entries 10, 13). The aldol reactions of β-MOM protected aldehyde **5a** with a given ketone are always more selective for aldol **7** than the reactions with the β-triethylsilyl ether protected aldehyde **5b** (compare entries 1 vs. 8; 3 vs. 9; 7 vs. 13, etc.). Moreover, the data show

Table 1. Aldol Reactions of 5 and 6



5a, R^3 = MOM
5b, R^3 = Et_3Si

6a, R^1 = Bn, R^2 = TBS
6b, R^1 = R^2 = TBS
6c, R^1 = TBS, R^2 = MPM

7, α-OH (Felkin diastereomer)
8, β-OH (anti-Felkin)

Entry	RCHO	Ketone	enolate (-78°C)[a]	Yield[b]	7 : 8
1	**5a**	**6a**	LHMDS, THF	76%	89 : 11
2	**5a**	**6a**	LHMDS, THF-HMPA	–	88 : 12
3	**5a**	**6a**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	74%	89 : 11
4	**5a**	**6a**	Bu_2BOTf, *i*-Pr_2NEt, Et_2O	44%	25 : 75
5	**5a**	**6b**	LHMDS, THF	77%	80 : 20
6	**5a**	**6b**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	45% (40%)	89 : 11
7	**5a**	**6b**	Bu_2BOTf, *i*-Pr_2NEt, Et_2O	56% (30%)	31 : 69
8	**5b**	**6a**	LHMDS, THF	65%	56 : 44
9	**5b**	**6a**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	67% (10%)	62 : 38
10	**5b**	**6a**	Bu_2BOTf, *i*-Pr_2NEt, Et_2O	51% (30%)	≤3 : 97
11	**5b**	**6b**	LHMDS, THF	64% (30%)	50 : 50
12	**5b**	**6b**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	28% (06%)	72 : 28
13	**5b**	**6b**	Bu_2BOTf, *i*-Pr_2NEt, Et_2O	40% (33%)	≤3 : 97
14	**5a**	**6c**	LHMDS, THF	45%	75 : 25
15	**5b**	**6c**	LHMDS, THF	82%	50 : 50
16	**5b**	**6c**	LHMDS, THF-HMPA	–	50 : 50
17	**5b**	**6c**	Bu_2BOTf, *i*-Pr_2NEt, Et_2O	59%	≤9 : 91

(a) Aldol reactions were performed by adding 1.0 equiv. of **5** to the enolate generated from 1.0 equiv. of **6**.
(b) The combined yields of **7** and **8** isolated by HPLC. Yields of recovered **6** are in parentheses.

that within each ketone-aldehyde pair, the reactions of the lithium and titanium enolates are consistently more selective for the Felkin diastereomer **7** than are the reactions of the corresponding enolborinates.[10]

The trends highlighted in Table 1 are further illustrated by the results of aldol reactions of aldehydes **5a-c** and isopropyl methyl ketone (Table 2, entries 1 - 16). Here also, excellent selectivity (97 : 3) for the Felkin aldol **6** is obtained by using a lithium enolate with aldehyde **2a** (R^3 = MOM; entries 1, 2), whereas the anti-Felkin diastereomer **7** is the near exclusive product (≤5 : 95) in the reaction of **2b** (R^3 = $SiEt_3$) and the enolborinate generated from *i*-PrCOMe (entry 15). Furthermore, selectivity for the anti-Felkin diastereomer **7** generally parallels the steric bulk of the ligands associated with the enolborinate (e.g., 9-BBN << Bu_2Bu) with a given aldehyde (entries 4, 5; 9, 10; 14, 15), as well as the steric bulk of the β-alkoxy group of **2** (MOM < $SiMe_3$ < $SiEt_3$) with a given enolate (e.g., entries 1, 7, 12 for Li; 5, 10 15 for Bu_2B-). While the dependence of aldol stereoselectivity on the aldehyde β-alkoxy group has been noted previously,[3a,c] our observation that the diastereoselectivity can be completely reversed simply by changing the enolate metal and the aldehyde β-alkoxy protecting group is unique.

The results of the aldol reactions of 2,3-anti aldehydes **5** may be rationalized if it is assumed that selectivity is determined by a competition between two major transition states: chair-like transition structure (t.s.) **14** that leads to the Felkin aldol diastereomers **7** and **9**, and boat-like t.s. **16** that leads to the anti-Felkin diastereomers **8** and **10**. It is known that boat-like transition structures are readily accessible in aldol reactions of methyl ketone enolates,[11] and we have previously argued that the anti-Felkin diastereomer (e.g., **8**, **10**) should be favored in aldol reactions that proceed by way of boat-like pathways owing to non-bonded interactions between the α-substituents on the aldehyde and the methyl ketone highlighted in **15**.[6b] Aldehydes **5** presumably adopt the conformation indicated in t.s. **14**

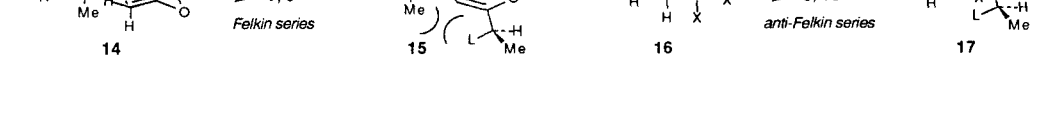
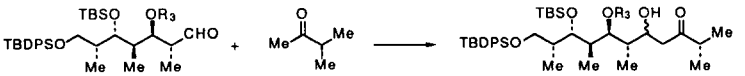
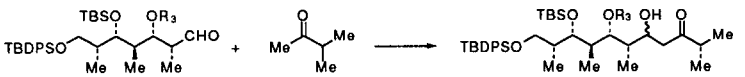


Table 2. Aldol Reactions of 5 and 11 with Isopropyl Methyl Ketone



5a, R^3 = MOM
5b, R^3 = Et_3Si
5c, R^3 = Me_3Si

9, α-OH (Felkin diastereomer)
10, β-OH (anti-Felkin)



11a, R^3 = MOM
11b, R^3 = Et_3Si

12, α-OH (Felkin diastereomer)
13, β-OH (anti-Felkin)

Entry	RCHO	enolate (-78°C) [a]	Yield	9 : 10
1	**5a**	LHMDS, THF	95%	97 : 3
2	**5a**	LHMDS, THF-HMPA	91%	97 : 3
3	**5a**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	88%	84 : 16
4	**5a**	9-BBNOTf, Et_3N, CH_2Cl_2	80%	75 : 25
5	**5a**	Bu_2BOTf, Et_3N, CH_2Cl_2	84%	62 : 38
6	**5a**	$(C_5H_9)_2BOTf$, Et_3N, CH_2Cl_2	72%	52 : 48
7	**5c**	LHMDS, THF	91%	79 : 21
8	**5c**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	73%	61 : 39
9	**5c**	9-BBNOTf, Et_3N, CH_2Cl_2	86%	59 : 41
10	**5c**	Bu_2BOTf, Et_3N, CH_2Cl_2	82%	10 : 90
11	**5c**	$(C_5H_9)_2BOTf$, Et_3N, CH_2Cl_2	49%	20 : 80
12	**5b**	LHMDS, THF	85%	66 : 34
13	**5b**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	74%	60 : 40
14	**5b**	9-BBNOTf, Et_3N, CH_2Cl_2	92%	40 : 60
15	**5b**	Bu_2BOTf, Et_3N, CH_2Cl_2	74%	≤5 : 95
16	**5b**	$(C_5H_9)_2BOTf$, Et_3N, CH_2Cl_2	78%	14 : 86

Entry			Yield [b]	12 : 13
17	**11a**	LHMDS, THF	74%	15 : 85
18	**11a**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	82%	62 : 38
19	**11a**	9-BBNOTf, Et_3N, CH_2Cl_2	82%	41 : 59
20	**11a**	Bu_2BOTf, Et_3N, CH_2Cl_2	69%	61 : 39
21	**11a**	$(C_5H_9)_2BOTf$, Et_3N, CH_2Cl_2	86%	50 : 50
22	**11b**	LHMDS, THF	85%	7 : 93
23	**11b**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	88%	27 : 73
24	**11b**	9-BBNOTf, Et_3N, CH_2Cl_2	36%(59)	50 : 50
25	**11b**	Bu_2BOTf, Et_3N, CH_2Cl_2	94%	45 : 55
26	**11b**	$(C_5H_9)_2BOTf$, Et_3N, CH_2Cl_2	77%	52 : 48

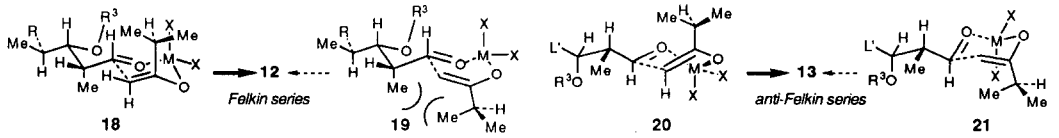
(a) Reactions were performed by adding 1.0 equiv. of **5** or **11** to the enolate generated from 2-2.5 equiv. of $Me_2CHCOMe$.
(b) The combined yields of **9-10** and **12-13** isolated by chromatography. Yield of recovered **11** is in parentheses.

since gauche pentane interactions along the carbon chain are minimized.[12] Analysis of rotational isomers about the C(3)-OR^3 bond then suggests that the protecting group R^3 occupies a position staggered between H(3) and C(2), as indicated in **10**. When R^3 is a bulky TES ether, one of the ethyl groups interacts with the axial metal ligand, X, as indicated by inspection of molecular models. Evidently, this interaction destabilizes **14** (and also **15**) relative to the anti-Felkin boat-like t.s. **16**, in which interactions between $SiEt_3$ and X are absent. The tendency for the anti-Felkin selectivity to increase as the size of the axial metal ligand increases (e.g., compare entries 1 and 4-6, Table 2) is also consistent with the involvement of R^3--X interactions in **14** that are absent in **16**. The destabilizing R^3--X interactions in **14** are relieved when R^3 is a MOM ether. The ability of the MOM group to adopt a conformation that directs the -CH_2OMe group way from X enables **14** to be increasingly competitive with **16**, especially when the O-Met and X-Met bonds are relatively long (e.g., lithium enolates).[13]

In contrast to the behavior of **5**, the results of aldol reactions of the 2,3-syn aldehyde **11** with isopropyl methyl ketone (Table 2, entries 17-26) show that the anti-Felkin aldol **13** is generally favored with Li and Ti enolates and that selectivity is enhanced with the bulky TES blocking group (Table 2, entries 17, 18; 22, 23). In all cases examined, the enolborinates of $Me_2CHCOMe$ undergo non-selective aldol reactions with **11** and show only modest dependence on the nature of R^3 or the steric demands of the ligands at boron.[14]

Examination of the transition states **18-21** available to **11** suggest that the chair-like t.s. **18** leading to the Felkin adduct **12** is destabilized by R^3O--carbonyl interactions (steric and dipole) analogous to those recently noted by Evans in nucleophilic additions to β-alkoxy aldehydes.[15] The observation that the lithium enolate aldol reactions are selective for the anti-Felkin adduct **13** argues for reaction via boat-like t.s. **20**, which should be favored as long as R^3--X contacts are minimized. The tendency of enolborinate aldol reactions of **11** to be non-selective suggests that R^3--X interactions increase in magnitude in **20** when M= BR_2 (analogous to the situation with **14**), such that the chair-like Felkin t.s. **18** becomes more competitive, in spite of the R^3O--carbonyl interactions.

In conclusion, we have established that the stereoselectivity of methyl ketone aldol reactions is highly dependent on the 2,3-stereochemistry of the chiral aldehyde, the aldehyde β-alkoxy protecting group, and the metal



enolate. We have also have presented arguments that the stereoselectivity can be rationalized by a competition between chair-like and boat-like transition structures. The most critical stereochemical control feature appears to be three dimensional orientation of the β-alkoxy protecting group (R^3) relative to the aldol six-centered cyclic transition state. It is important to recognize that the orientation of -OR^3 in the transition structures may differ from the conformations presented here as the steric requirements and stereochemistry of adjacent substituents vary (e.g., R in **14** and **18**).[12,16] It is imperative, therefore, that complete conformational analyses of all possible transition structures be performed when attempting to predict the outcome of methyl ketone aldol reactions.

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8. (a) The stereochemistry of the aldol products (R^3 = MOM) was determined by ^{1}H NMR analysis of methylene acetals generated by treatment with Me_2BBr and 2,6-di-*tert*-butyl-4-methylpyridine. Stereochemistry of aldols with R^3 = TMS or TES was assigned following desilylation and hemiketal formation. (b) Control experiments established that the lithium enolate aldol reactions reported herein are kinetically controlled.
9. The different behavior of **5** vs. **2** implies that the stereochemical change at C(5) interfers with formation of the eight-membered chelate transition state **4**. A detailed analysis will be presented in our full paper.
10. Aldol reactions the Li, Ti and B enolates of **6a** and **6b** with isobutyraldehyde indicate that the intrinsic diastereofacial bias of the chiral methyl ketone is rather low: selectivities range from 70 : 30 in favor of the (S)-aldol with Ti enolates, to 18 : 82 in favor of the (R)-aldol with the Bu_2B- enolate.
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