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Reversal of Selectivity in Acetate Aldol Reactions of *N*-Acetyl-(*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one

Gopal L. Khatik, Varun Kumar, and Vipin A. Nair*

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, Mohali, Punjab 160 062, India

vn74nr@yahoo.com; vnair@niper.ac.in

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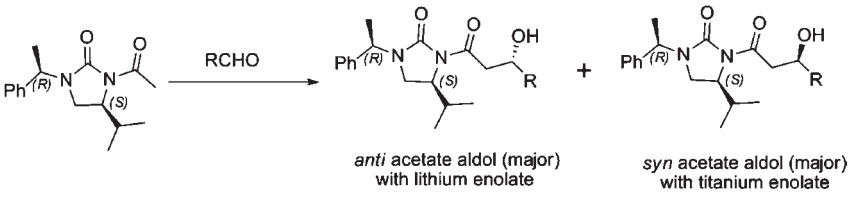
ABSTRACT



Synergistic effects of the exo- and endocyclic chiral centers of an imidazolidinone-based auxiliary were investigated in the perspective of acetate aldol reactions. The reversal in diastereoselectivity was accomplished by lithium and titanium enolate reactions, which proceed through proposed open and closed transitions states, respectively. The aldol adducts were used in the stereoselective synthesis of fluoxetine.

The importance of aldol reactions in C−C bond formation with one or many chiral centers is widely recognized and is valuable for the synthesis of bioactive molecules and natural products.[1] For selective generation of chirality in aldol reactions, a variety of chiral auxiliaries were developed in the last three decades, including the oxazolidinones by Evans.[2] However, meager diastereomeric ratios for the acetate aldol reaction, nucleophilic ring-opening of the oxazolidinone,[3] and endocyclic cleavage during the removal of the auxiliary by alkaline hydrolysis paved the way for continued interest in the development of newer auxiliaries.[4] The objective of good stereoselection in acetate aldol reactions has found success with chiral acetate enolates of tin,[5] lithium,[6] boron,[7] and titanium[8] but still endures copious drawbacks including extremely low reaction temperature for satisfactory diastereoselectivity,[6] an

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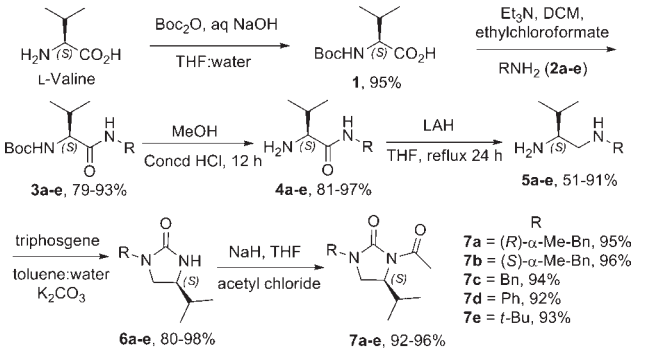
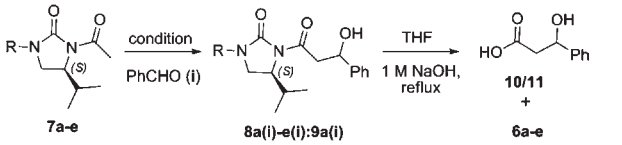
Scheme 1. Synthesis of Compounds (**7a**−**e**)



expensive metal source like tin(II) triflate[5] or *n*-dibutylboryl triflate,[2] lower levels of stereoselectivity with aryl aldehydes,[8c] and aliphatic aldehydes.[8e] The use of commercially expensive (−)-sparteine with $TiCl_4$ affords higher selectivities, while the mechanistic details are unclear.[8e,f,9]

To address the predicament of acetate aldol reactions, we focused our efforts on the development of a chiral auxiliary[10f] based on our current interests in heterocyclic scaffolds and reaction methodology.[10] A simple synthetic strategy was adopted from a less expensive starting material for the preparation of the auxiliary (Scheme 1). L-Valine (**1**) protected with Boc anhydride was coupled with amines, either chiral or achiral (**2a**−**e**). Deprotection by HCl and reduction of the amide using lithium aluminum hydride (LAH) afforded the diamines **5a**−**e**, which were cyclized using triphosgene, to obtain the chiral auxiliaries **6a**−**e**. The auxiliaries were acetylated (**7a**−**e**) and further investigated for acetate aldol reactions with benzaldehyde (Table 1). It was anticipated that, with chiral amines, the exocyclic chiral center generated at the *N*3 position of the auxiliary, and the resident endocyclic chiral center at *C*5, would play a synergistic role in governing the stereoselectivity of the enolate reactions at *N*1. Among the different bases employed for a typical

Table 1. Acetate Aldol Reactions of **7a**−**e** with Benzaldehyde



entry	compd	condition	yield[a] (%)	dr **8:9** (*anti*:*syn*)[b]	β-hydroxy acid[e]
1	**7a**	*n*-BuLi[c]	nil		
2	**7a**	LDA[c]	70	95:05	(+)-(*S*), **10**
3	**7a**	LiHMDS[c]	92	99:01	(+)-(*S*), **10**
4	**7a**	NaHMDS[c]	78	99:01	(+)-(*S*), **10**
5	**7a**	KHMDS[c]	40	99:01	(+)-(*S*), **10**
6	**7b**	LiHMDS[c]	90	99:01	(+)-(*S*), **10**
7	**7c**	LiHMDS[c]	76	95:05	(+)-(*S*), **10**
8	**7d**	LiHMDS[c]	71	95:05	(+)-(*S*), **10**
9	**7e**	LiHMDS[c]	81	97:03	(+)-(*S*), **10**
10	**7a**	$TiCl_4$[d]	90	04:96	(−)-(*R*), **11**

[a] Yield corresponds to major aldol isomer. [b] Ratio was determined from ^{1}H NMR (400 MHz) of the crude product. [c] Base (1.1 equiv), THF, −78 °C, 1 h, PhCHO (1.1 equiv), 1 h. [d] $TiCl_4$ (2.0 equiv), DIPEA (1.0 equiv), DCM, −78 °C, 1 h, PhCHO (1.1 equiv), 30 min. [e] Configuration was determined by correlating the specific rotation with the literature data.[10f,11]

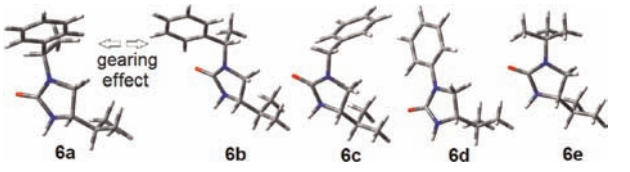


Figure 1. Most stable conformation of *N*3-substituted chiral auxiliaries [(*R*)-α-Me-Bn (**6a**), (*S*)-α-Me-Bn (**6b**), Bn (**6c**), Ph (**6d**), *t*-Bu (**6e**)] optimized using basis set B3LYP/STO-3G.

reaction of **7a** with benzaldehyde, LiHMDS afforded excellent yield of the aldol adduct. However, with LiHMDS as the base for further optimizations, the other variants at *N*3 (*t*-Bu, Ph, Bn, and (*S*)-α-Me-Bn) had an intriguing impact on the selectivity. A *tert*-butyl, phenyl, or benzyl substituent at *N*3 afforded modest yield of the product with a reasonably good selectivity of 95:05 to 97:03 favoring the *anti* acetate aldol adduct (entries 7−9, Table 1). However with an (*R*)/(*S*)-α-Me-Bn substituent at *N*3 the yield improved dramatically with a highly appreciable *anti* aldol selectivity of 99:01 (entries 3 and 6, Table 1). Interestingly, the configuration at this chiral center did not bear any influence on the product stereochemistry as both the enantiomers of the α-Me-Bn group afforded almost similar yields and same selectivity. Thus, the α-Me-Bn group was found to significantly influence the stereoelectronic factors enhancing the enolate reactivity, apart from providing the steric biasness. Switching over to the Lewis acid, titanium tetrachloride demonstrated a reversal in diastereoselectivity toward the *syn* acetate aldol adduct (*anti*:*syn* = 04:96, entry 10, Table 1).

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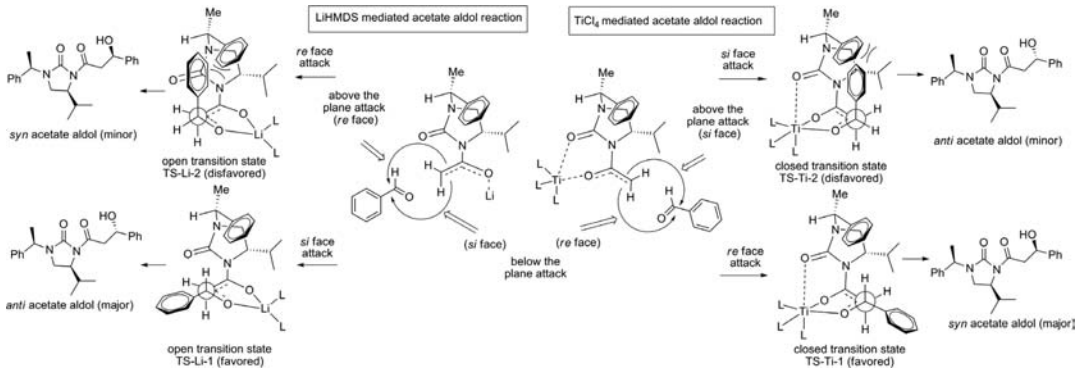

Figure 2. Possible transition states for lithium- and titanium-mediated acetate aldol reaction.

To understand the stereochemical implications, ab initio molecular orbital calculations were carried out using basis set B3LYP/STO-3G levels on a Gaussian03 program package,[12] and the most stable conformation was identified (Figure 1) for each of the chiral auxiliaries **6a**−**e**. This was extrapolated to the corresponding acetate derivatives **7a**−**e**. The proposed transition states for the reaction between **7a** and benzaldehyde, analogous to the transition states computed by Shinisha et al.,[13] are depicted in Figure 2. Lithium coordinates with the carbonyl groups of the acetyl substituent on *N*1 and the aldehyde allowing a six membered open transition state, similar to boron enolate.[2,14a] The transition state TS-Li-1 is favored over TS-Li-2 due to comparatively less steric repulsion on the Cα-*si* face of aldehyde, affording the *anti* acetate aldol as the major product.

Contrary to this, titanium forms the chlorotitanium enolate, which is expected to proceed through a closed transition state as a result of chelation promoted by the oxophilicity.[8a] A six-membered transition state TS-Ti-1 involving carbonyl groups of the auxiliary, acetyl substituent at *N*1 and aldehyde,[8a,14] is favored over TS-Ti-2 due to comparatively less steric repulsion on the Cα-*re* face of aldehyde affording the *syn* acetate aldol as the major product. This validates our inferences on the additional directive influence of the *N*3-α-Me-Bn group of **7a** and **7b**, which is geared to favor a Cα-*si* face attack over Cα-*re* face attack on the electrophile in an open transition state, while it would be the reverse in the case of a closed transition state. The lower selectivity observed with **7c**, **7d**, and **7e** may be due to the lack of this gearing effect.

The lithium enolate of **7a** was examined for acetate aldol reactions with various aryl/heteroaryl aldehydes (**i**−**ix**), and excellent selectivity toward the *anti* acetate aldol adducts was obtained (Table 2). Reaction with *trans*-cinnamaldehyde (**x**) at −78 °C afforded high diastereoselectivity (02:98, *syn:anti*), whereas isobutyraldehyde (**xi**) gave moderate selectivity (30:70, *syn:anti*). To improve the selectivity, the reaction temperature was reduced to −90 °C, and we found appreciable enhancement in diastereoselectivity (11:89, *syn:anti*). This optimized reaction condition was utilized in the acetate aldol reactions with other aliphatic aldehydes such as isovaleraldehyde (**xii**), pivaldehyde (**xiii**), and phenylacetaldehyde (**xiv**) (entries 12−14, Table 2). The reversal of selectivity observed with the Lewis acid $TiCl_4$ was further assessed with various aldehydes (**i**−**xiv**), affording the *syn* acetate aldol adducts in good yields and selectivities.

The acetate aldol reaction was then explored for the stereoselective formation of (*S*)- and (*R*)-fluoxetine. The fluoxetine racemate (Prozac) is marketed as a potent selective serotonin reuptake inhibitor (SSRI), but the enantiomers exhibit different pharmacological properties.[15] (*R*)-Fluoxetine is used for treating depression, while (*S*)-fluoxetine is envisaged for migraine treatment. Chirality has been introduced in fluoxetine synthesis through enantioselective hydroxylation,[16] epoxidation,[17] chemical[18] and enzymatic[19] reduction of ketones and

(12) All calculations were performed using the Gaussian 03 program package: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. In Gaussian03, Revision E.01; Gaussian, Inc.: Wallingford CT, 2004.

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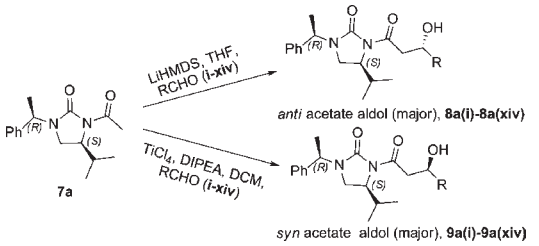
Table 2. Acetate Aldol Reaction with Aldehydes Using Lithium Enolate and Titanium Enolate of **7a**



entry	RCHO	lithium enolate[a] yield[c] (%)	lithium enolate[a] dr **9:8** (*syn*:*anti*)[d]	titanium enolate[b] yield[c] (%)	titanium enolate[b] dr **9:8** (*syn*:*anti*)[d]
1	C_6H_5CHO	92	01:99	90	96:04
2	4−F-C_6H_4CHO	90	01:99	84	95:05
3	4−Cl-C_6H_4CHO	86	01:99	86	95:05
4	2−Cl-C_6H_4CHO	86	01:99	83	95:05
5	4−Br-C_6H_4CHO	89	01:99	88	95:05
6	4-Me-C_6H_4CHO	86	01:99	80	98:02
7	2-MeO-C_6H_4CHO	91	01:99	70	95:05
8	furfural	80	01:99	78	95:05
9	thiophene-2-carboxaldehyde	78	01:99	69	95:05
10	*trans*-cinnamaldehyde	95	02:98	86	94:06
11	isobutyraldehyde	82	11:89[e]	78	90:10[e]
12	isovaleraldehyde	89	05:95[e]	91	96:04[e]
13	pivaldehyde	90	08:92[e]	85	93:07[e]
14	phenylacetaldehyde	79	07:93[e]	82	96:04[e]

[a] LiHMDS (1.1 equiv), THF, −78 °C, 1 h, RCHO (1.1 equiv), 1 h. [b] $TiCl_4$ (2.0 equiv), DIPEA (1.0 equiv), DCM, −78 °C, 1 h, RCHO (1.1 equiv), 30 min. [c] Yield corresponds to major isomer. [d] Ratio was determined from ^{1}H NMR (400 MHz) of the crude product. [e] Reaction temperature −90 °C.

β- ketoesters, and stereoselective coupling reaction using chiral auxiliary or chiral catalyst.[20] We attempted a simple procedure for the synthesis of both the enantiomers of fluoxetine by taking advantage of the reversal of selectivity observed with the lithium and titanium enolates

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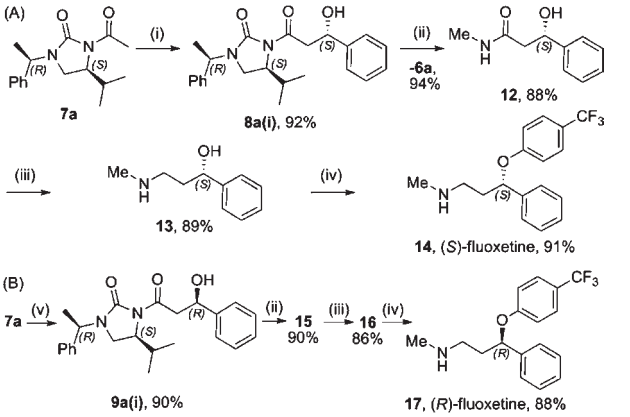
Scheme 2. Stereoselective Synthesis of (*S*)-Fluoxetine (A) and (*R*)-Fluoxetine (B)[a]



[a] Conditions: (i) LiHMDS, THF, −78 °C, PhCHO; (ii) aq $MeNH_2$, MeOH, reflux, 4 h; (iii) LAH, THF, reflux, 6 h; (iv) NaH, DMA, 90 °C, 30 min, 4-fluorobenzotrifluoride, 100 °C, 3 h; (v) $TiCl_4$, DIPEA, DCM, −78 °C, PhCHO.

(Scheme 2). Compound **7a** affords *anti* acetate aldol [**8a(i)**] with LiHMDS, which was converted to (*S*)-3-hydroxy-*N*-methyl-3-phenyl propanamide **12** upon direct treatment with methyl amine and subsequent cleavage from the auxiliary. The amide was reduced with LAH and then subjected to nucleophilic aromatic substitution on 4-fluorobenzotrifluoride[17a] to afford (*S*)-fluoxetine in excellent yield and enantiopurity. When **7a** was treated with $TiCl_4$, *syn* acetate aldol [**9a(i)**] was obtained, which was transformed to afford (*R*)-fluoxetine using a similar protocol as described for (*S*)-fluoxetine.

To conclude, the reversal of selectivity, and synergistic effects of the chiral centers of an imidazolidinone based auxiliary were explored in acetate aldol reactions.

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Note Added after ASAP Publication. Figure 2 contained errors in the version published ASAP May 9, 2012, the correct version reposted May 18, 2012.

Supporting Information Available. Experimental, computational studies, and analytical data of the compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.