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Stereoselective Titanium-Mediated Aldol Reactions of a Chiral Lactate-Derived Ethyl Ketone with Ketones

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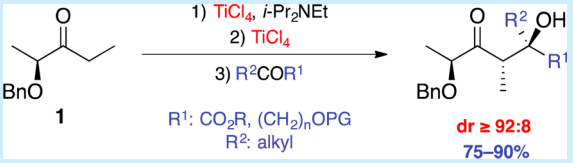
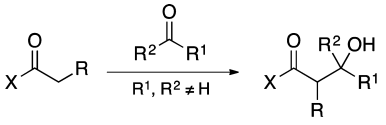
Supporting Information

ABSTRACT: Aldol reactions of titanium enolates of lactate-derived ethyl ketone **1** with other ketones proceed in a very efficient and stereocontrolled manner provided that a further equivalent of $TiCl_4$ is added to the reacting mixture. The scope of these reactions encompasses simple ketones such as acetone or cyclohexanone as well as other ketones that contain potential chelating groups such as pyruvate esters or α- and β-hydroxy ketones.



The breathtaking accomplishments on the asymmetric aldol addition to aldehydes reported over the last decades have placed the aldol reaction among the most important transformations in organic synthesis.[1] In contrast, parallel additions to ketones are much less common.[2] Ironically, a milestone in organic synthesis such as the proline-catalyzed Eder–Sauer–Wiechert–Hajos–Parrish reaction[3] involves an *intramolecular* aldol addition to a ketone, but apart from this case,[4] stereoselective and *intermolecular* aldol reactions in which a ketone acts as the electrophilic partner are hitherto scarce. The reasons for this lack of a synthetic methodology are thermodynamic and structural; especially important in hindering the development of such processes are the attenuated reactivity of ketones and the similarity of the two groups flanking the carbonyl bond compared to aldehydes.[5,6] Thus, it is not surprising that most of the approaches reported up to now deal with asymmetric *acetate* aldol additions (R = H, in Scheme 1) to α-keto esters and other activated ketones.[7,8]

Scheme 1. Aldol Additions to Ketones



Despite these achievements, the simultaneous installation of a tertiary and a quaternary stereocenter associated with the *propionate* counterparts (R = CH_3, in Scheme 1) still remains elusive,[9] and the few procedures reported so far are only suitable for a very small group of ketones.[7a,10,11]

Considering that stereocontrol of these reactions may be achieved by using reactive and well-ordered intermediates, we envisaged that titanium enolates from chiral α-hydroxy ketones might permit such challenging transformations.[12] Indeed, previous reports from our laboratory have established that an appropriate choice of the hydroxyl protecting group and the titanium(IV) Lewis acid provides highly stereoselective aldol additions to aldehydes.[13] Specifically, the use of 2 equiv of $TiCl_4$ has proven to be crucial for attaining notable levels of stereocontrol in aldol reactions from methyl,[14] ethyl,[15] and even isopropyl chiral ketones.[16] Herein, we describe the successful application of these ideas to the substrate-controlled aldol reactions of lactate-derived ethyl ketone **1**[17] (Table 1) with other ketones, which now provides new access to the stereoselective synthesis of aldol adducts possessing two contiguous tertiary and quaternary stereocenters.

Preliminary experiments showed that the reaction of the titanium enolates of **1** with acetone (**2a**) did not occur at low temperatures. Higher temperatures and 2 equiv of $TiCl_4$ were required to obtain diastereoselectively (dr 95:5) the aldol adduct **3a** with a 35% yield (compare entries 1–4 in Table 1). Longer reaction times increased the yield without eroding the diastereoselectivity, and 75% of adduct **3a** was finally isolated after 15 h at −20 °C (entry 5 in Table 1). Cyclohexanone (**2b**) produced similar results (entry 6 in Table 1), but unfortunately, acetophenone (**2c**) and 3-methyl-2-butanone (**2d**) possessing different R^1 and R^2 groups afforded the corresponding adducts **3c** and **3d** as an equimolar mixture of two diastereomers in moderate yields (entries 7 and 8 in Table 1). These results proved the feasibility of our approach but also highlighted the daunting challenge of aldol additions to nonactivated ketones. We therefore paid special attention to pyruvate esters, which are often chosen as model substrates because the ester group enhances the electrophilicity of the ketone and the structural differences between the carboxylate and the methyl groups facilitate the π-facial discrimination of the carbonyl bond. Needless to say, they can also form rigid and highly activated complexes with bidentate Lewis acids that are ideally suited for diastereoselective reactions with nucleophiles.

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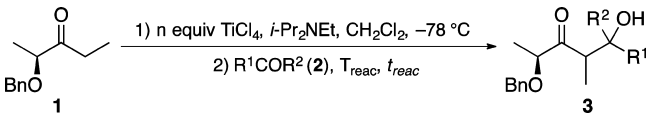
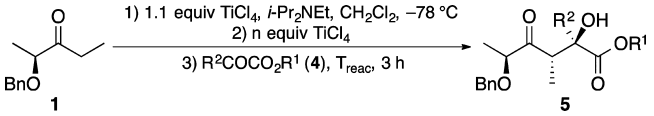
Table 1. Titanium-Mediated Aldol Additions of Lactate-Derived Ethyl Ketone 1 to Nonactivated Ketones 2



entry	$TiCl_4$ equiv (n)	ketone	R^1	R^2	T_{reac} (°C)	$time_{reac}$ (h)	aldol	dr[a]	yield[b] (%)
1	1.1	**2a**	Me	Me	−78	3	**3a**		
2	2.2	**2a**	Me	Me	−78	3	**3a**		
3	1.1	**2a**	Me	Me	−20	3	**3a**	nd	<5
4	2.2	**2a**	Me	Me	−20	3	**3a**	95:5	35
5	2.2	**2a**	Me	Me	−20	15	**3a**	95:5	75
6	2.2	**2b**	$(CH_2)_5$		−20	15	**3b**	95:5	75
7	2.2	**2c**	Me	Ph	−20	72	**3c**	50:50[c]	50
8	2.2	**2d**	Me	*i*-Pr	−20	72	**3d**	50:50[c]	39

[a]Established by ^{1}H NMR analysis. [b]Overall isolated yield. [c]Only two of up to four diastereomers are observed in the reaction mixture by ^{1}H NMR analysis.

Table 2. Titanium-Mediated Aldol Additions of Lactate-Derived Ethyl Ketone 1 to α-Keto Esters 4



entry	α-keto ester	R^1	R^2	$TiCl_4$ (*n* equiv)	T_{reac} (°C)	aldol	dr[a]	yield[b] (%)
1	**4a**	Et	Me		−78	**5a**	83:17	(46)
2	**4a**	Et	Me		−20	**5a**	82:18	(87)
3	**4a**	Et	Me	1.1	−78	**5a**	97:3	88
4	**4a**	Et	Me	1.1	−20	**5a**	97:3	87
5	**4b**	Me	Me	1.1	−20	**5b**	97:3	91
6	**4c**	Bn	Me	1.1	−20	**5c**	97:3	84
7	**4d**	*i*-Pr	Me	1.1	−20	**5d**	98:2	84
8	**4e**	*t*-Bu	Me	1.1	−20	**5e**	98:2	79
9	**4f**	Et	$PhCH_2CH_2$	1.1	−20	**5f**	98:2	91
10	**4g**	Et	*i*-Bu	1.1	−20	**5g**	98:2	86
11	**4h**	Et	$PhCH_2$	1.1	−20	**5h**	98:2	68
12	**4i**	Et	*i*-Pr	1.1	−20	**5i**	85:15	68 (80)
13	**4i**	Et	*i*-Pr	1.1	−78	**5i**	85:15	52 (62)[c]

[a]Established by ^{1}H NMR and HPLC analysis. [b]Isolated yield of diastereomer **5**. Overall yield is shown in parentheses. [c]30% of ketone **1** is recovered.

Since previous tests had shown the crucial role of Lewis acid, we initially assessed the influence of the equivalents of $TiCl_4$ and the temperature on the aldol addition of **1** to ethyl pyruvate (**4a**). We were pleased to observe that the reaction proceeded at −78 °C without requiring a supplementary amount of Lewis acid, albeit with a moderate yield and moderate diastereoselectivity (46% and dr 83:17, entry 1 in Table 2). Interestingly, the yield was enhanced by performing the reaction at −20 °C without adverse effect on the diastereoselectivity (87% and dr 82:18, entry 2 in Table 2). Following thorough optimization, it was finally established that the addition of a further equivalent of $TiCl_4$ to the reaction mixture produced aldol **5a** in high yields with complete stereocontrol (dr 97:3) both at −78 and −20 °C (entries 3 and 4 in Table 2); this suggested that the success with these reactions required the addition of this second equivalent of $TiCl_4$. Encouraged by these findings, we decided to assess the scope of this reaction in the substitution pattern on the α-keto ester backbone.

To that end, we applied the optimized conditions to a range of α-keto esters (**4** in Table 2).[18] Aldol additions to pyruvate esters **4a−e** (R^2 = Me) produced all the adducts **5a−e** in diastereomeric ratios up to 98:2 with a 80−90% yield irrespective of the steric bulk of the R^1 group (entries 4−8 in Table 2). However, the diastereoselectivity was sensitive to the steric hindrance of the R^2 group. Ethyl esters **4f** and **4g** without bulky substituents (R^2 = $PhCH_2CH_2$ and *i*-Bu, respectively) gave a single diastereomer (dr 98:2) in excellent yields (entries 9 and 10 in Table 2), as did the easily enolizable α-keto ester **4h** (R^2 = $PhCH_2$), which furnished aldol **5h** with a 68% yield (entry 11 in Table 2). In contrast, sterically hindered ethyl 3-methyl-2-oxobutanoate (**4i**, R^2 = *i*-Pr) produced an 85:15 mixture of two diastereomers at both −20 and −78 °C with a moderate-to-good overall yield (entries 12 and 13 in Table 2).

The configuration of the aldols **5** was firmly established by X-ray diffraction of lactone **6**,[19] prepared from **5a** by removing the benzyl protecting group followed by lactonization of the resultant hydroxy ester (Scheme 2).[20]

Aiming to expand the scope of the process, we next evaluated the reactivity of protected α- and β-hydroxy methyl ketones **7**.[21] As for α-keto esters, the outcome of the reactions of alkoxy ketones **7a−c** turned out to be closely related to the amount of Lewis acid used in the process. Indeed, preliminary studies showed that the yield steadily increased when a further equivalent of $TiCl_4$ was added to the reaction mixture (compare entries 1−6 in Table 3). This was particularly remarkable for β-benzyloxy ketone **7c**, which emphasizes the

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Scheme 2. Configuration of Aldols 5

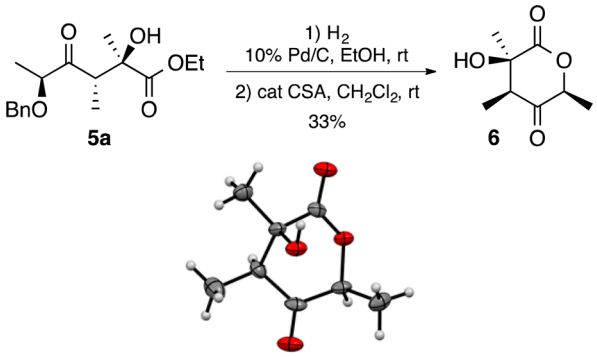
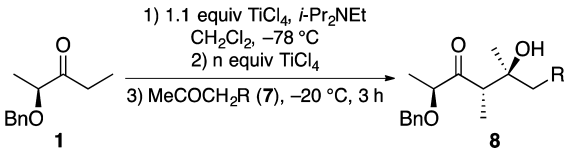


Table 3. Titanium-Mediated Aldol Additions of 1 to α- and β-Hydroxy Methyl Ketones 7



entry	ketone	R	aldol	$TiCl_4$ (*n* equiv)	dr[a]	yield[b] (%)
1	7a	OMe	8a		90:10	44
2	7a	OMe	8a	1.1	95:5	63
3	7b	OBn	8b		97:3	60
4	7b	OBn	8b	1.1	97:3	88
5	7c	CH_2OBn	8c		55:45	(8)
6	7c	CH_2OBn	8c	1.1	92:8	(80)
7	7d	OTBS	8d	1.1	95:5	77
8	7e	OTBDPS	8e	1.1	69:31	(57)
9	7f	OTIPS	8f	1.1	73:27	(58)

[a]Established by ^1H NMR analysis. [b]Isolated yield of diastereomer **8**. Overall yield is shown in parentheses.

crucial role of carbonyl activation in these processes. More importantly, the stereocontrol of this reaction was dramatically improved from a roughly equimolar mixture of two diastereomers (dr 55:45) to aldol adduct **8c** (dr 92:8) by the simple addition of an extra equivalent of $TiCl_4$ (compare entries 5 and 6 in Table 3).[22] Briefly, application of these conditions to alkoxy ketones **7a–c** afforded diastereoselectively the corresponding adducts **8a–c** in high yield irrespective of the position, α or β, of the alkoxy group (entries 2, 4, and 6 in Table 3). Finally, we assessed the reaction of structurally related α-silyloxy ketones **7d–f**. The results, summarized in Table 3, show that the stereocontrol with these ketones depends on the silicon protecting group.[23] Indeed, TBS-ketone **7d** afforded adduct **8d** in a slightly lower yield than the OBn-ketone **7b** (compare entries 4 and 7 in Table 3), whereas the more bulky TBDPS and TIPS groups in ketones **7e** and **7f** produced approximately 70:30 mixtures of two diastereomers in moderate yields (entries 8 and 9 in Table 3). Although the mechanism of the reaction is still under scrutiny, all these results suggest that ketones containing chelating groups (esters or ethers) may undergo highly stereoselective titanium-mediated aldol reactions from **1** provided that a further equivalent of $TiCl_4$ is added to the reaction mixture.

In summary, the aldol addition of titanium enolates from lactate-derived ethyl ketone **1** to ketones can proceed with a remarkable stereocontrol and high yields. The scope of such a substrate-controlled reaction encompasses structurally simple ketones such as acetone or cyclohexanone as well as α-keto esters and α- or β-hydroxy ketones. This highlights the crucial role of chelating groups in π-facial discrimination of the carbonyl bond.

■ ASSOCIATED CONTENT

Supporting Information

Physical and spectroscopic data for aldol adducts **3a,b**, **5a–i**, and **8a–d** and proof of the stereochemistry of **5a** and **8c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of Francisco Sánchez Baeza.

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(18) Pyruvate esters **4a** and **4b** are commercially available. In turn, α-keto esters **4c−i** were prepared following standard procedures reported in the literature; see: (a) Hegarty, A. F.; O'Neill, P. *Synthesis* **1993**, 606. (b) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. *Tetrahedron* **2005**, *61*, 6249.

(19) Crystallographic data for **6** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-971401. A copy of the data can be obtained free of charge on application to CCDC (e-mail: deposit@ccdc.cam.ac.uk).

(20) A single diastereomer of lactone **6** was observed through the cyclization reaction.

(21) Ketones **7a** and **7c** are commercially available. Benzyloxy ketone **7b** was prepared from benzyl propargyl ether; see: Boger, D. L.; Palanki, M. S. S. *J. Am. Chem. Soc.* **1992**, *114*, 9318. In turn, α-silyloxy ketones **7d−f** were prepared by standard treatments of hydroxyacetone.

(22) The relative *anti* configuration of **8c** has been secured through debenzylation and NMR analyses of the resultant hemiketal. See the Supporting Information.

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