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

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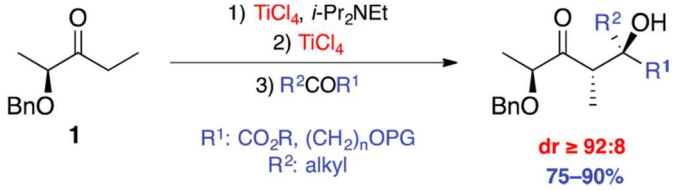
ABSTRACT

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 TiCl4 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 reaction3 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 Despite these achievements, the simultaneous installation of a tertiary and a quaternary stereocenter associated with the propionate counterparts (R = CH3, 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 TiCl4 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 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 TiCl4 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 R1 and R2 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.

Since previous tests had shown the crucial role of Lewis acid, we initially assessed the influence of the equivalents of TiCl4 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 TiCl4 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 TiCl4. 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 (R2 = 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 R1 group (entries 4−8 in Table 2). However, the diastereoselectivity was sensitive to the steric hindrance of the R2 group. Ethyl esters 4f and 4g without bulky substituents (R2 = PhCH2CH2 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 (R2 = PhCH2), which furnished aldol 5h with a 68% yield (entry 11 in Table 2). In contrast, sterically hindered ethyl 3-methyl-2-oxobutanoate (4i, R2 = 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 Xray 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 TiCl4 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 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 TiCl4 (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 titaniummediated aldol reactions from 1 provided that a further equivalent of TiCl4 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.

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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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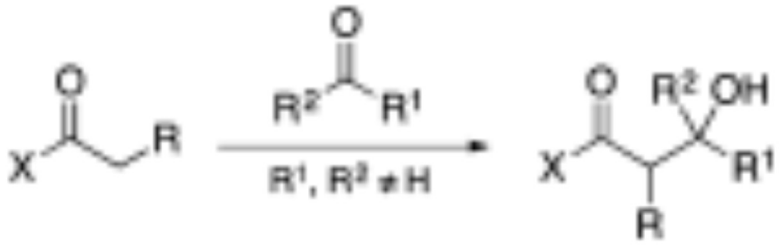
Legends to figures

Scheme 1. Aldol Additions to Ketones

Scheme 2. Configuration of Aldols 5

SCHEME 1



255 **SCHEME 2**

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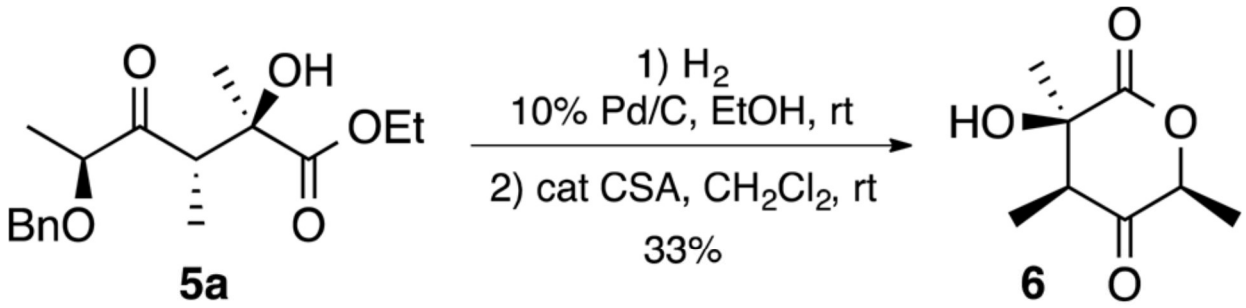

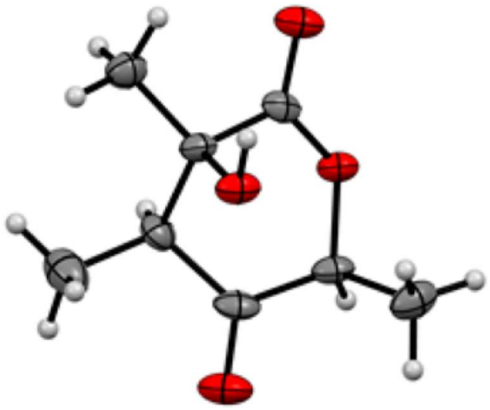

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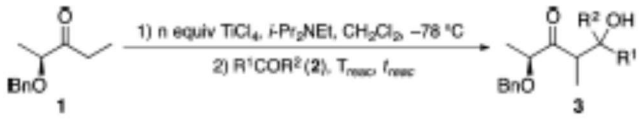
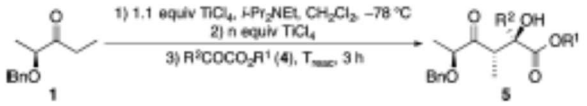
Table 1. Titanium-Mediated Aldol Additions of Lactate-Derived Ethyl Ketone 1 to Nonactivated Ketones 2



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

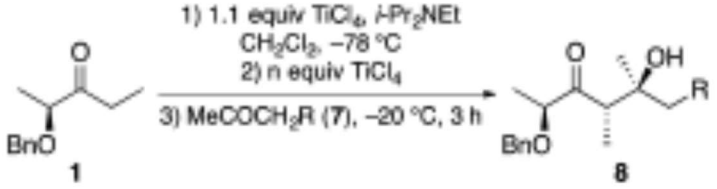
Table 2. Titanium-Mediated Aldol Additions of Lactate-Derived Ethyl Ketone 1 to α-Keto Esters 4



entry	α-keto ester	R^1	R^2	$TiCl_4$ (*n* equiv)	T_{max} (°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 ^1H NMR and HPLC analysis. [b] Isolated yield of diastereomer 5. Overall yield is shown in parentheses. [c] 30% of ketone 1 is recovered.

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.