Substrate-Controlled Michael Additions of Chiral Ketones to Enones

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ABSTRACT

Substrate-controlled Michael additions of the titanium-(IV) enolate of lactate-derived ketone 1 to acyclic α,β-unsaturated ketones in the presence of a Lewis acid (TiCl4 or SnCl4) provide the corresponding 2,4-anti-4,5-anti dicarbonyl compounds in good yields and excellent diastereomeric ratios. Likely, the nucleophilic species involved in such additions are bimetallic enolates that may add to enones through cyclic transition states. Finally, further studies indicate that a structurally related β-benzyloxy chiral ketone can also participate in such stereocontrolled conjugate additions.

Comprehensive studies carried out in the 1980s on the conjugate addition of metal enolates to α,β-unsaturated compounds, the venerable Michael reaction, provided a reasonably good understanding of the key elements that determine the relative configuration of the resultant adducts.1,2 Despite these early achievements and the ensuing exploitation of this transformation in the synthesis of natural products, there is still a shortage of asymmetric Michael methodologies.3,4 Highly enantioselective catalyzed intermolecular additions of esters or ketones to α,β-unsaturated compounds have recently been reported, but they only cover a small range of substrates. Indeed, their scope is usually restricted to the most easily enolizable carbonyl compounds and the best acceptors; furthermore, just a few of them have succeeded in the simultaneous installation of two new chiral centers (R1 ≠ R2 and R3 ≠ R4 in Scheme 1).5,6

Therefore, the stereoselective construction of 1,5-dicarbonyl structures through conjugate intermolecular additions of simple carbonyl derivatives to α,β-unsaturated ketones or esters is still a challenging transformation. In this context, classical chiral auxiliary-like approaches based on chiral hydrazines7 or oxazolidinones8 have been reported, but their scope is often narrower than that attained in other representative C−C bondforming reactions. Moreover, and to the best of our knowledge, no substrate-controlled Michael reactions from chiral ketones have been reported to date. Considering that highly reactive titanium(IV) enolates could fill this void, we envisaged that substrate-controlled Michael additions of titanium(IV) enolates from lactate-derived α-benzyloxy ethyl ketone 19 to enones might produce 1,5-diketones containing up to two new stereocenters. Herein, we describe conjugate additions of titanium enolates of 1 to a wide range of enones in the presence of a second equivalent of a Lewis acid. These reactions give the corresponding adducts in a highly stereocontrolled manner and good yield.

Preliminary experiments showed that the dibutylboron enolate from 1 was unable to undergo conjugate additions to methyl vinyl ketone (a) and the starting material 1 was recovered unchanged even after long reaction times (entry 1, Table 1). In turn, the lithium enolate counterpart turned out to be more reactive, but it only afforded tiny amounts of the Michael adduct 2a (entry 2, Table 1).10−12 Thus, we were pleased to observe that the titanium(IV) enolate of 1 afforded 2a as a single diastereomer, albeit in a low 23% yield (entry 3, Table 1).13 Encouraged by such an outstanding stereocontrol and taking advantage of our experience with these titanium enolates, we assessed the influence of a second equivalent of TiCl4.14 Under these conditions, the reaction with 1.2 equiv of a proceeded smoothly and 2a was obtained with excellent diastereoselectivity (dr >97:3) and yields of 70% and 80% after 2 and 5 h respectively (entries 4 and 5, Table 1). Longer reaction times, higher temperatures, and a higher loading of enone did not improve this result (entries 4−7, Table 1). Instead, such conditions led to a more elaborate Michael adduct (3a), arising from the subsequent conjugate addition of a putative titanium enolate intermediate. It was obtained in variable yields and with a moderate diastereoselectivity (entries 6 and 7, Table 1). Importantly, the addition of the second equivalent of TiCl4 at the beginning of the enolization (see entries 4−7 of Table 1) simplified the experimental procedure.

Having recognized the crucial role of the second equivalent of TiCl4, other Lewis acids were also tested.15 Unfortunately, most of them proved to be less suitable. The stereocontrol was excellent and a single diastereomer was obtained for these Lewis acids, but the yields dropped with the exception of SnCl4. Indeed, both the yield and diastereoselectivity achieved by adding 1 equiv of SnCl4 to the titanium(IV) enolate of 1 were the same as those achieved with TiCl4 (dr >97:3 and 80% yield). This suggests that a similar intermediate may be responsible for the stereocontrolled outcome of both Lewis acid mediated Michael additions.

Once the feasibility of the conjugate addition had been established (see Table 1), we examined the scope of the reaction using vinyl ketones b−e16 (Table 2). Thus, we were pleased to observe that all these additions produced pure Michael adducts 2a−e as single diastereomers in isolated yields of up to 80%

(Table 2). Interestingly, the addition to α-silyloxy chiral vinyl ketone e proceeded smoothly to afford the corresponding Michael adduct 2e in 78% yield. Altogether, these results confirm the potential of such an approach for the stereoselective synthesis of 1,5-diketones. The successful Lewis acid mediated Michael addition of 1 to a broad range of vinyl ketones led us to assess the parallel reaction with β-substituted enones,17 which involves the formation of a new chiral center. Conventional wisdom predicted that the introduction of an alkyl group in the β-position would reduce the reactivity of the Michael acceptor and provoke a certain loss of stereocontrol. Thus, it was no surprise that the previous experimental conditions failed with (E)-4-penten-3-one (f). Indeed, the expected Michael adduct 4f was obtained in a low 17% yield and 90:10 diastereomeric ratio (entry 1, Table 3). Following thorough optimization, it was found that an increase of the reaction temperature facilitated the conjugate addition and dramatically improved the yields of 4f without producing any loss of stereocontrol (entries 1−3, Table 3). Importantly, the use of SnCl4 instead of TiCl4 as a second Lewis acid afforded 4f in slightly lower yields but with a 94:6 diastereomeric ratio at both −40 and −20 °C (entries 1−5, Table 3). Such an advantageous effect was also observed for enone g (entries 6 and 7, Table 3), although the addition of SnCl4 was detrimental for enone h because of the partial removal of the TBS protecting group. For this ketone, TiCl4 was more convenient and afforded the Michael adduct 4h in 68% yield and 90:10 diastereomeric ratio (entry 8, Table 3). In turn, the addition to (E)-4-phenyl-3-buten-2-one (i) proceeded smoothly and afforded diastereoselectively (dr 90:10) the expected Michael adduct 4i in 83% yield (entry 9, Table 3). Hence, the Lewis acid mediated conjugate additions of titanium(IV) enolate of 1 to acyclic β-substituted enones afforded the 2,4-anti-4,5-anti Michael adducts 4f−i in good yields and high diastereomeric ratios (dr ≥90:10). Unfortunately, such a conjugate addition proved to be unsuitable for cyclic enones. Cyclopentenone afforded complex mixtures under different conditions whereas cyclohexenone produced the Michael adducts with a 71% yield but poor diastereoselectivity (dr 65:35).

The configuration of Michael adducts 2 was initially established through conversion of 2b into a known keto ester.18 Later, the stereochemical outcome of these additions was corroborated through X-ray analysis of adduct 4i (Figure 1),19 which confirmed that the configuration of C3 was the same as that obtained in adducts 2.

Although the need for a further equivalent of TiCl4 or SnCl4 was firmly identified, the precise role of this second Lewis acid was still elusive. The study by NMR of the enolate involved in such reactions indicated that its structure is dramatically affected by the addition of TiCl4 or SnCl4, but a clear image did not emerge from these experiments. Thus, taking advantage of our experience and based on models proposed by other authors, we hypothesize that a bimetallic enolate arising from the association of the second Lewis acid to the titanium Z enolate20 might be the real nucleophilic species involved in these additions. Then, two alternative pictures based on Heathcock's model21 are envisioned (Scheme 2). The first one calls for a coordination in which the incoming Lewis acid is placed far from the nucleophilic center. Then, we speculate that further coordination of the α,β-unsaturated ketone to the titanium center of the bimetallic enolate I will trigger the C−C bond formation through a cyclic transition state in which the Re face of the enolate attacks the Si face of the enone (Scheme 2). Conversely, a more compact bimetallic enolate II might also result from such an association. This second proposal requires that the α,β-unsaturated ketone binds to the metal center M to proceed through a parallel cyclic transition state to that involved in the former pathway. A similar model has been proposed by Wang22 to rationalize the Lewis acid mediated Michael additions of titanium enolates derived from diazo ketocarbonyl compounds. Regardless of the true structure of the nucleophilic species, both models account for the outstanding stereocontrol at C3 and C4 chiral centers as well as the poor diastereoselectivity shown by cyclic enones.

Finally, the excellent results achieved in the Lewis acid mediated Michael addition from lactate-derived chiral ketone 1 led us to examine the scope of the method using other chiral ketones. Particularly, we focused our attention on ketone 5, which has been employed at length in other substratecontrolled processes. Titanium enolates derived from this ketone proved to be slightly less reactive than those from

1, but they reacted with α,β-unsaturated ketones a and f to provide the corresponding adducts 6a and 7f in a highly stereocontrolled manner (Scheme 3).23

In summary, substrate-controlled Michael additions of a chiral lactate-derived ethyl ketone to vinyl ketones and β-substituted enones proceed with good yields and excellent diastereoselectivities provided that a second equivalent of a Lewis acid ($TiCl4$ or $SnCl4$) is added to the reaction mixture. This method can also be applied to a structurally related β-benzyloxy ketone derived from the Roche ester, which proves the wide scope of such a process for the stereoselective synthesis of 1,5-dicarbonyl compounds. Likely, a bimetallic enolate might be responsible for the outstanding stereocontrol achieved in these substrate-controlled Michael additions.

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Notes

The authors declare no competing financial interest.

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(15) Lewis acids as BF3·OEt2, MgBr2·OEt2, Et2AlCl, Ti(i-PrO)4, and SnCl4 were also tested.

(16) Ketones a and b are commercially available. Ketones c−e were prepared as reported, see: Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. Synlett 1997, 1414−1416. (17) Enones f and i are commercially available. Enones g and h were prepared by standard acetone-based Wittig reactions.

(18) See the Supporting Information.

(19) Crystallographic data for 4i has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1013203. A copy of the data can be obtained free of charge on application to CCDC (E-mail: deposit@ccdc.cam.ac.uk).

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(23) The absolute configuration of 6a has been established by chemical correlation (see the Supporting Information). The configuration of 7f has been assigned by analogy.

Legends to figures

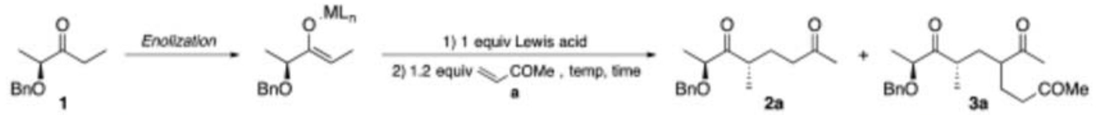
Scheme 1. Michael Additions of Metal Enolates

Figure 1. X-ray structure of adduct 4i.

Scheme 2. Plausible Mechanism for the Michael Addition of the Titanium Enolate of 1 to α,β-Unsaturated Ketones

Scheme 3. Michael Additions from β-Benzyloxy Ketone 5

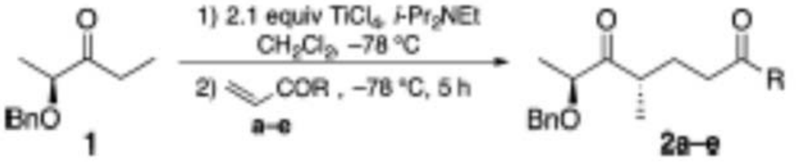
Table 1. Michael Addition of Titanium(IV) Enolate of 1 to Methyl Vinyl Ketone (a)



entry	M	Lewis acid	temp (°C)	time (h)	dr[a] 2a	yield 2a (%)[b]	dr[c] 3a	yield 3a (%)[b]
1	BBu_2	–	−20	15	–	–	–	–
2	Li	–	−78	2	–	<10	–	–
3	$TiCl_4$	–	−78	2	>97:3	23	–	–
4	$TiCl_4$	$TiCl_4$	−78	2	>97:3	70	–	–
5	$TiCl_4$	$TiCl_4$	−78	5	>97:3	80	–	–
6	$TiCl_4$	$TiCl_4$	−40	2	>97:3	47	80:20	16
7[d]	$TiCl_4$	$TiCl_4$	−78	2	>97:3	53	80:20	13

[a] The minor diastereomer was not detected in the reaction crude mixtures by ^{1}H NMR (400 MHz). [b] Isolated yield. [c] Diastereomeric ratio established by ^{1}H NMR (400 MHz). [d] 2.5 equiv of enone a were used.

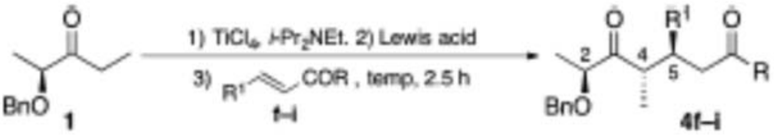
Table 2. $TiCl_4$-Mediated Michael Addition of Titanium(IV) Enolate of 1 to Vinyl Ketones

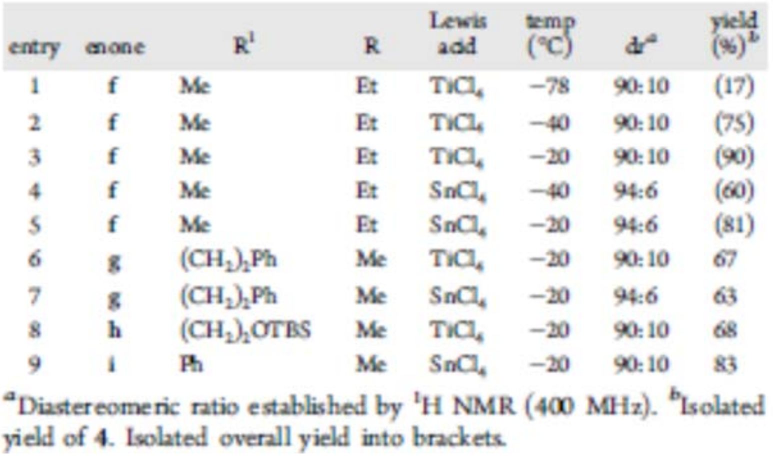


entry	enone	R	dr[a]	yield (%)[b]
1	**a**	Me	>97:3	80
2	**b**	Et	>97:3	79
3	**c**	$(CH_2)_2Ph$	>97:3	75
4	**d**	*c*-hex	>97:3	73
5[c]	**e**	(*S*)-CH(OTBS)Bn	>97:3	78

[a] The minor diastereomer was not detected in the reaction crude mixtures by ^1H NMR (400 MHz). [b] Isolated yield. [c] Reaction time of 2 h.

Table 3 Lewis Acid Mediated Michael Addition of Titanium Enolate of 1 to β-Substituted Enones





entry	enone	R¹	R	Lewis acid	temp (°C)	dr[a]	yield (%)[b]
1	f	Me	Et	$TiCl_4$	−78	90:10	(17)
2	f	Me	Et	$TiCl_4$	−40	90:10	(75)
3	f	Me	Et	$TiCl_4$	−20	90:10	(90)
4	f	Me	Et	$SnCl_4$	−40	94:6	(60)
5	f	Me	Et	$SnCl_4$	−20	94:6	(81)
6	g	$(CH_2)_2Ph$	Me	$TiCl_4$	−20	90:10	67
7	g	$(CH_2)_2Ph$	Me	$SnCl_4$	−20	94:6	63
8	h	$(CH_2)_2OTBS$	Me	$TiCl_4$	−20	90:10	68
9	i	Ph	Me	$SnCl_4$	−20	90:10	83

[a]Diastereomeric ratio established by ^1H NMR (400 MHz). [b]Isolated yield of 4. Isolated overall yield into brackets.

Scheme

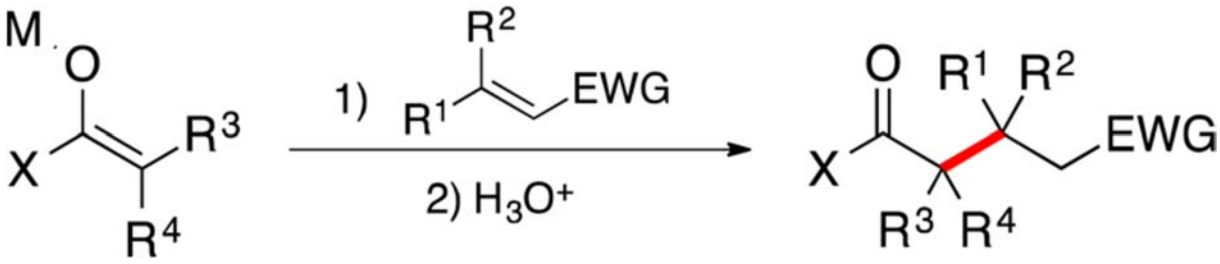
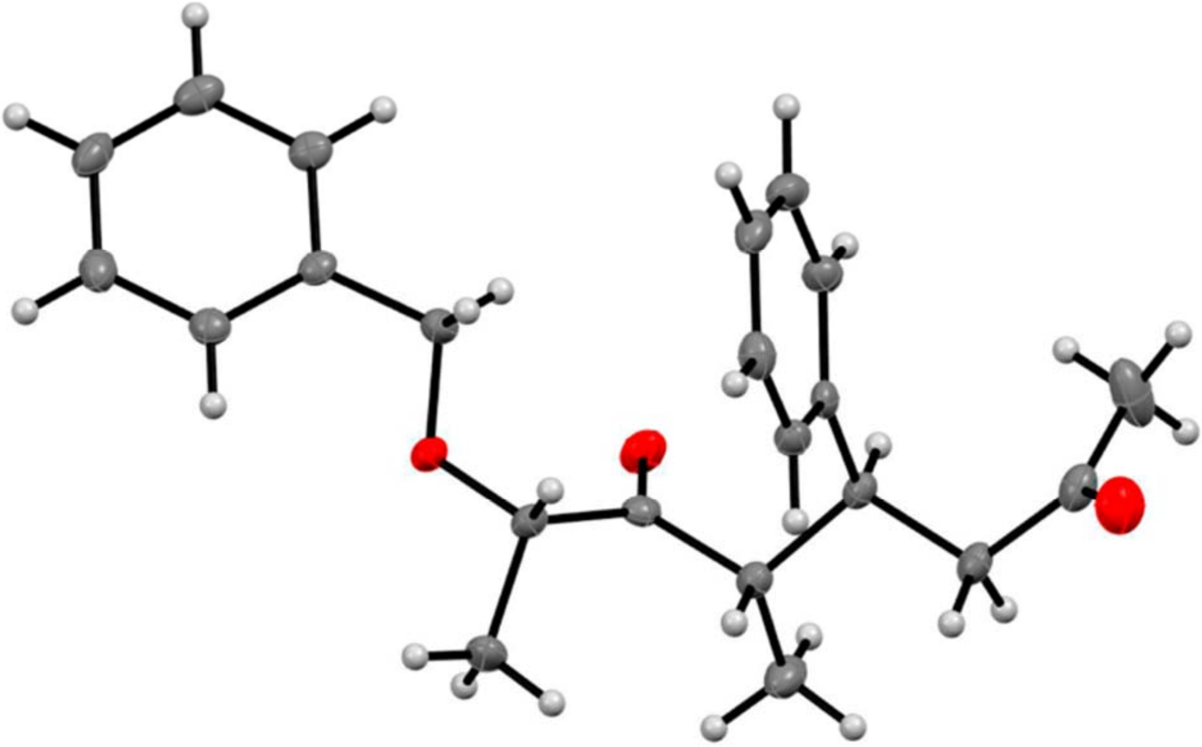
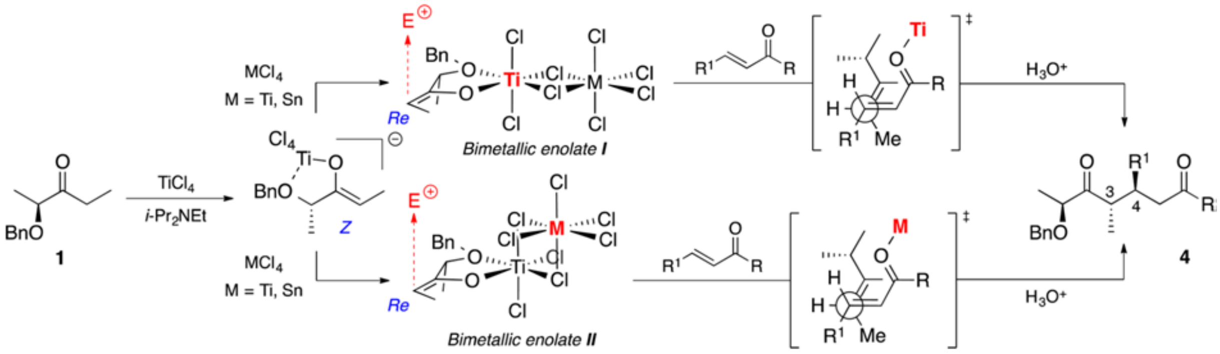


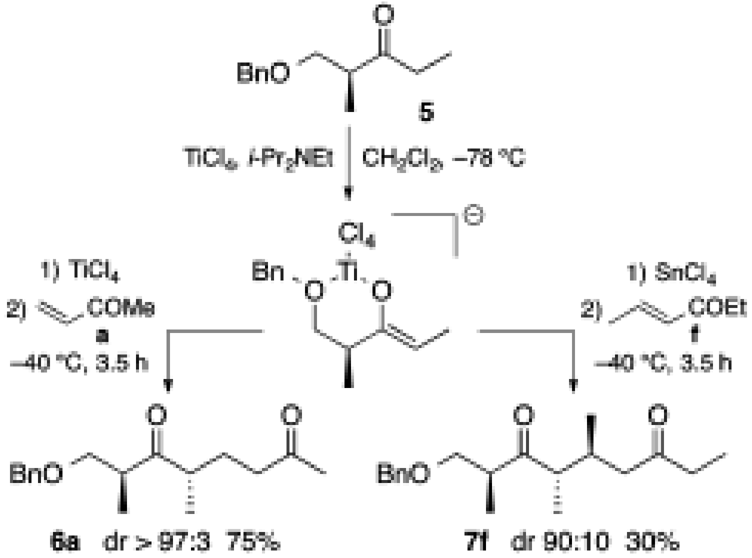
Figure 1



Scheme 2


1
TiCl4
i-Pr2NEt
Z
MCl4
M = Ti, Sn
E⊕
Re
Bimetallic enolate I
Bimetallic enolate II
H3O+
‡
4
3
4

Scheme 3


BnO
O
5
TiCl$_4$, i-Pr$_2$NEt
CH$_2$Cl$_2$, −78 °C
Cl$_4$
Bn
Ti
O
O
⊖
1) TiCl$_4$
2) COMe
a
−40 °C, 3.5 h
1) SnCl$_4$
2) COEt
f
−40 °C, 3.5 h
BnO
O
O
6a dr > 97:3 75%
BnO
O
O
7f dr 90:10 30%