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5 **Substrate-Controlled Michael Additions of Chiral Ketones to Enones**
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27 **ABSTRACT**

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29 Substrate-controlled Michael additions of the titanium-(IV) enolate of lactate-derived ketone 1 to
30 acyclic α,β -unsaturated ketones in the presence of a Lewis acid (TiCl_4 or SnCl_4) provide the
31 corresponding 2,4-anti-4,5-anti dicarbonyl compounds in good yields and excellent diastereomeric
32 ratios. Likely, the nucleophilic species involved in such additions are bimetallic enolates that may add
33 to enones through cyclic transition states. Finally, further studies indicate that a structurally related β -
34 benzyloxy chiral ketone can also participate in such stereocontrolled conjugate additions.

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39 Comprehensive studies carried out in the 1980s on the conjugate addition of metal enolates to α,β -
40 unsaturated compounds, the venerable Michael reaction, provided a reasonably good understanding of
41 the key elements that determine the relative configuration of the resultant adducts.^{1,2} Despite these early
42 achievements and the ensuing exploitation of this transformation in the synthesis of natural products,
43 there is still a shortage of asymmetric Michael methodologies.^{3,4} Highly enantioselective catalyzed
44 intermolecular additions of esters or ketones to α,β -unsaturated compounds have recently been reported,
45 but they only cover a small range of substrates. Indeed, their scope is usually restricted to the most easily
46 enolizable carbonyl compounds and the best acceptors; furthermore, just a few of them have succeeded
47 in the simultaneous installation of two new chiral centers ($R_1 \neq R_2$ and $R_3 \neq R_4$ in Scheme 1).^{5,6}

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

59 Preliminary experiments showed that the dibutylboron enolate from 1 was unable to undergo conjugate
60 additions to methyl vinyl ketone (a) and the starting material 1 was recovered unchanged even after long
61 reaction times (entry 1, Table 1). In turn, the lithium enolate counterpart turned out to be more reactive,
62 but it only afforded tiny amounts of the Michael adduct 2a (entry 2, Table 1).^{10–12} Thus, we were
63 pleased to observe that the titanium(IV) enolate of 1 afforded 2a as a single diastereomer, albeit in a low
64 23% yield (entry 3, Table 1).¹³ Encouraged by such an outstanding stereocontrol and taking advantage
65 of our experience with these titanium enolates, we assessed the influence of a second equivalent of
66 TiCl_4 .¹⁴ Under these conditions, the reaction with 1.2 equiv of a proceeded smoothly and 2a was
67 obtained with excellent diastereoselectivity (dr >97:3) and yields of 70% and 80% after 2 and 5 h
68 respectively (entries 4 and 5, Table 1). Longer reaction times, higher temperatures, and a higher loading
69 of enone did not improve this result (entries 4–7, Table 1). Instead, such conditions led to a more
70 elaborate Michael adduct (3a), arising from the subsequent conjugate addition of a putative titanium
71 enolate intermediate. It was obtained in variable yields and with a moderate diastereoselectivity (entries
72 6 and 7, Table 1). Importantly, the addition of the second equivalent of TiCl_4 at the beginning of the
73 enolization (see entries 4–7 of Table 1) simplified the experimental procedure.

74 Having recognized the crucial role of the second equivalent of TiCl_4 , other Lewis acids were also
75 tested.¹⁵ Unfortunately, most of them proved to be less suitable. The stereocontrol was excellent and a
76 single diastereomer was obtained for these Lewis acids, but the yields dropped with the exception of
77 SnCl_4 . Indeed, both the yield and diastereoselectivity achieved by adding 1 equiv of SnCl_4 to the
78 titanium(IV) enolate of 1 were the same as those achieved with TiCl_4 (dr >97:3 and 80% yield). This
79 suggests that a similar intermediate may be responsible for the stereocontrolled outcome of both Lewis
80 acid mediated Michael additions.

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

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

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

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

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

133 1, but they reacted with α,β -unsaturated ketones a and f to provide the corresponding adducts 6a and 7f
134 in a highly stereocontrolled manner (Scheme 3).²³

135 In summary, substrate-controlled Michael additions of a chiral lactate-derived ethyl ketone to vinyl
136 ketones and β -substituted enones proceed with good yields and excellent diastereoselectivities provided
137 that a second equivalent of a Lewis acid (TiCl_4 or SnCl_4) is added to the reaction mixture. This method
138 can also be applied to a structurally related β -benzyloxy ketone derived from the Roche ester, which
139 proves the wide scope of such a process for the stereoselective synthesis of 1,5-dicarbonyl compounds.
140 Likely, a bimetallic enolate might be responsible for the outstanding stereocontrol achieved in these
141 substrate-controlled Michael additions.

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149 **Notes**

150 The authors declare no competing financial interest.

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214 reactions.
- 215 (18) See the Supporting Information.
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- 226 (23) The absolute configuration of 6a has been established by chemical correlation (see the
227 Supporting Information). The configuration of 7f has been assigned by analogy.
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229 **Legends to figures**

230

231 **Scheme 1.** Michael Additions of Metal Enolates

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

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

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238 **Scheme 3.** Michael Additions from β -Benzyloxy Ketone 5

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

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entry	M	Lewis acid	temp (°C)	time (h)	dr ^a 2a	yield 2a (%) ^b	dr ^c 3a	yield 3a (%) ^b
1	BBr ₄	—	-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

^aThe minor diastereomer was not detected in the reaction crude mixtures by ¹H NMR (400 MHz). ^bIsolated yield. ^cDiastereomeric ratio established by ¹H NMR (400 MHz). ^d2.5 equiv of enone **a** were used.

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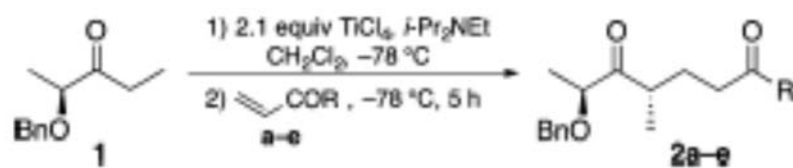
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247 **Table 2.** TiCl₄-Mediated Michael Addition of Titanium(IV) Enolate of **1** to Vinyl Ketones

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entry	enone	R	dr ^a	yield (%) ^b
1	a	Me	>97:3	80
2	b	Et	>97:3	79
3	c	(CH ₂) ₂ Ph	>97:3	75
4	d	<i>c</i> -hex	>97:3	73
5 ^c	e	(<i>S</i>)-CH(OTBS)Bn	>97:3	78

^aThe minor diastereomer was not detected in the reaction crude mixtures by ¹H NMR (400 MHz). ^bIsolated yield. ^cReaction time of 2 h.

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

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entry	enone	R ¹	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) ₂ Ph	Me	TiCl ₄	-20	90:10	67
7	g	(CH ₂) ₂ Ph	Me	SnCl ₄	-20	94:6	63
8	h	(CH ₂) ₂ OTBS	Me	TiCl ₄	-20	90:10	68
9	i	Ph	Me	SnCl ₄	-20	90:10	83

^aDiastereomeric ratio established by ¹H NMR (400 MHz). ^bIsolated yield of **4**. Isolated overall yield into brackets.

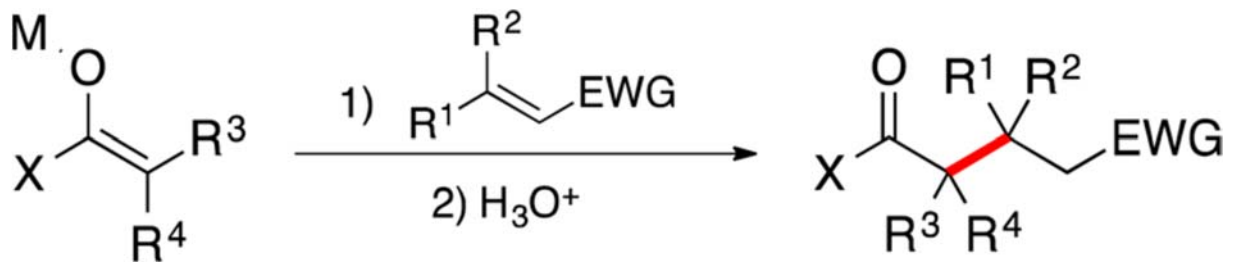
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Scheme

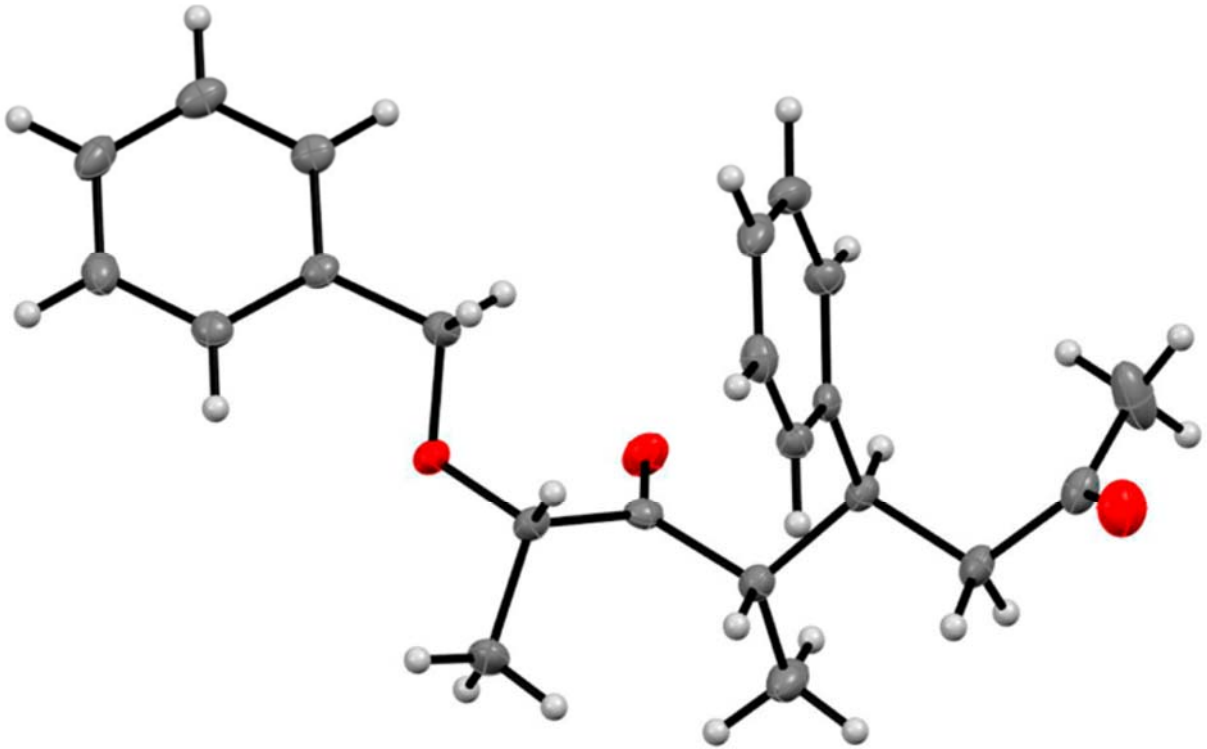


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Figure 1

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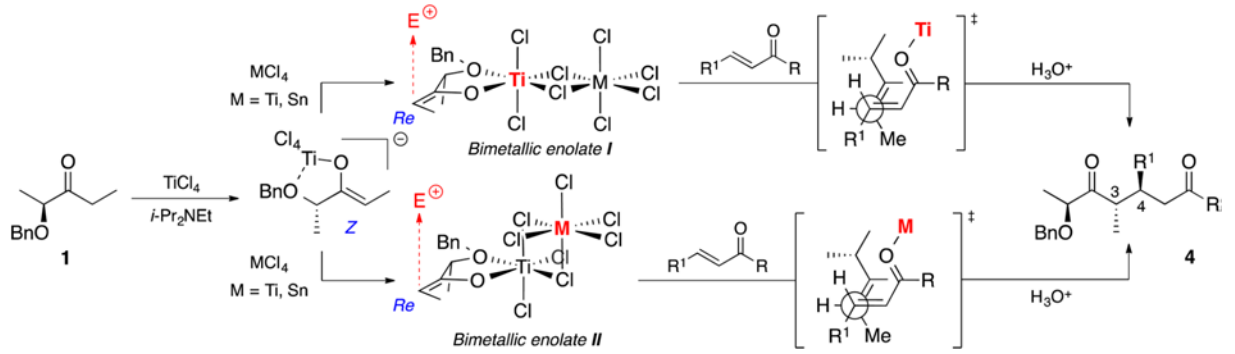
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Scheme 2

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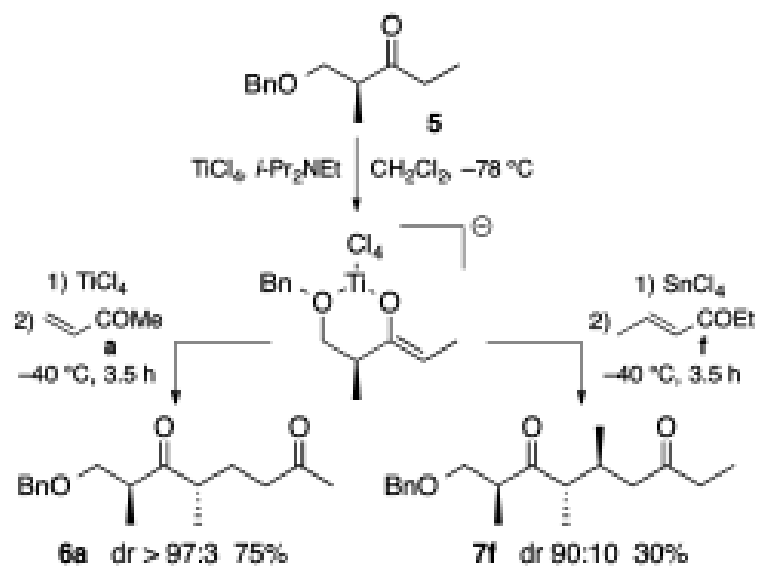
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Scheme 3

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