

## Diastereocontrol in the Reaction of Amide-homoenolates with Aromatic Aldehydes

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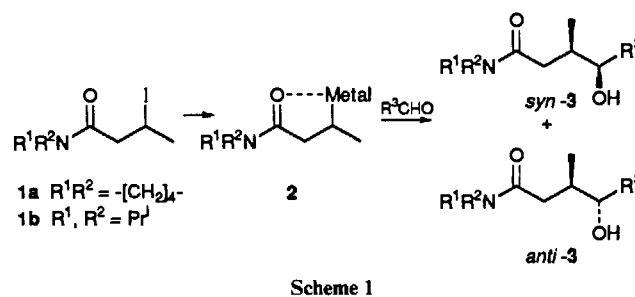
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The reaction of chiral Ti<sup>IV</sup> amide-homoenolates with aromatic aldehydes gave *syn*-adducts predominantly, whereas the corresponding Zn<sup>II</sup> reagents in the presence of chlorotrimethylsilane gave the *anti*-adducts preferentially.

Stereocontrolled reactions with chiral organometallic reagents are of indisputable importance in asymmetric synthesis.<sup>1</sup> Though there are many reports on stereocontrol with chiral enolates, allyl-metal reagents and related species, only few examples with simple chiral organometallic reagents have appeared.<sup>2</sup> In this paper, we describe our preliminary results on diastereocontrol in the homo-Reformatsky and related reactions<sup>3</sup> with *sec*-homoenolates under various conditions.

Amide-homoenolates **2** were chosen since the high chelating ability of amides was expected to result in a high stereoselectivity. The amide-homoenolates were generated by Knochel's method<sup>4</sup> and reacted with aldehydes *via* titanium reagents by applying Ochiai's method<sup>5</sup> (Method A). A high degree of *syn*-selectivity was observed (Table 1, entries 1–5).

Inversion of diastereoselectivity by a change in reaction mode was then envisioned. Initially, the reaction of the zinc amide-homoenolates **2** (Metal = ZnI), generated in THF by Knochel's method, with benzaldehyde by using BF<sub>3</sub>·OEt<sub>2</sub> or chlorotrimethylsilane as an activator was examined, however, the reaction did not work.<sup>6</sup> In examining the reaction conditions, we found that the zinc amide-homoenolate can be easily prepared with activated zinc<sup>7</sup> in CH<sub>2</sub>Cl<sub>2</sub> in the presence of 0.05–0.1 equiv. of chlorotrimethylsilane at room temperature for 0.5–1 h. The corresponding ester-homoenolate could not be prepared by the same method. The generated zinc amide-homoenolates were found to react with aromatic aldehydes in the presence of chlorotrimethylsilane. For example, the homoenolates reacted with benzaldehyde at room temperature exothermically in the presence of 2 equiv. of chlorotrimethylsilane to give *anti*-**3** preferentially (entries 6 and 7).<sup>8</sup> Other aromatic aldehydes also gave *anti*-adducts preferentially (entries 8–10). In the silyl reagents examined, iodotrimethylsilane and trimethylsilyl trifluoromethanesulfonate were also effective, however, chlorotriethylsilane was less effective and *tert*-butylchlorodimethylsilane was ineffective. In the range of 0–40 °C, the reaction temperature did not affect the *anti*:*syn* ratios. The reaction of acetophenone with the zinc amide-



homoenolates under the above reaction conditions resulted in failure. Transformation of adducts into lactones was also examined. Though the treatment of the diastereoisomerically pure *anti*-**3b** (R<sup>3</sup> = Ph) with a catalytic amount of *p*-TsOH gave a diastereoisomeric mixture of lactones, treatment with 6 equiv. of CF<sub>3</sub>CO<sub>2</sub>H in THF at reflux for 18.5 h gave the diastereoisomerically pure *anti*-lactone in quantitative yield.

In summary, we have demonstrated for the first time that preferential formation of each diastereoisomer is possible in the reactions of chiral amide-homoenolates and aromatic aldehydes.

### Experimental

**Typical Procedure (Method B).**—To a mixture of the iodide **1** (3 mmol) and activated Zn<sup>7</sup> (3.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 cm<sup>3</sup>) was added chlorotrimethylsilane (0.3 mmol). The mixture was stirred at room temperature for 1 h, whilst the consumption of the iodide **1** was monitored by TLC [hexane–EtOAc (1:1); **1b**, R<sub>f</sub> 0.56]. The relevant aldehyde (2.1 mmol) and further chlorotrimethylsilane (6 mmol) were then added to the mixture, which was stirred for 0.5–3 h at room temperature and then diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with water. Purification by silica gel column chromatography or preparative TLC with ethyl acetate–hexane as eluent gave the pure *syn*-**3** and *anti*-**3**

Table 1 Diastereoselective reactions of the homoenolate **2** with several aromatic aldehydes

Entry	<b>1</b>	R <sup>3</sup>	Method <sup>a</sup>	Time (h)	Yield <b>3</b> (%)	Ratio <i>syn</i> : <i>anti</i>
1	<b>1a</b>	Ph	A	3	80	97:3
2	<b>1b</b>	Ph	A	3	79	94:6
3	<b>1b</b>	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	A	3	87	85:15
4	<b>1b</b>	2-Furyl	A	0.5	61	96:4
5	<b>1b</b>	1-Naphtyl	A	14	59	91:9
6	<b>1a</b>	Ph	B	2.5	72	19:81
7	<b>1b</b>	Ph	B	2.5	82	13:87
8	<b>1b</b>	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	B	0.6	95	25:75
9	<b>1b</b>	2-Furyl	B	0.6	60	38:62
10	<b>1b</b>	1-Naphtyl	B	2.5	84	21:79

<sup>a</sup> Method A: Metal = Ti(OPr<sup>i</sup>)<sub>3</sub>, THF, 0 °C–room temp.; Method B: Metal = ZnI, 2 equiv. Me<sub>3</sub>SiCl, CH<sub>2</sub>Cl<sub>2</sub>, room temp.

adducts [hexane-EtOAc (1:1): *syn*-**3b** ( $R^3 = \text{Ph}$ ),  $R_f$  0.37; *anti*-**3b** ( $R^3 = \text{Ph}$ ),  $R_f$  0.33] or a mixture of the two. Yields were based on the aldehydes and the diastereoisomeric ratios were determined by  $^1\text{H}$  NMR (270 MHz) analysis of the crude product.

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