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# Diethyl zinc catalyzed diastereoselective addition of ketenes to (S)-(+)-3-hydroxytetrahydrofuran

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Abstract—The reaction of (S)-(+)-3-hydroxytetrahydrofuran with phenyl methyl ketene in presence of *n*-BuLi and Et<sub>2</sub>Zn results in the formation of the diastereomeric esters (SS+SR) with a high degree of diastereoselectivity (98:2). © 2001 Elsevier Science Ltd. All rights reserved.

We first demonstrated the synthesis<sup>1,2</sup> of (S)-(+)-3hydroxytetrahydrofuran and its stereoselective reactions via chiral sulfonyl methyl isocyanides.<sup>3</sup> It has been used in 1,4-chirality transfer cycloaddition reactions<sup>4</sup> as well as in the asymmetric synthesis of (S)-(+)-atrolactic acid.<sup>5</sup> Both the (R)-(-)- and (S)-(+)-enantiomers of 3-hydroxytetrahydrofuran have been used for the synthesis of potent HIV protease inhibitors.<sup>6</sup>

The catalytic asymmetric addition of an achiral alcohol to a chiral ketene in the presence of optically active bases is known to result in an efficient asymmetric synthesis of esters,<sup>7</sup> whereas uncatalyzed addition of a chiral alcohol to a chiral ketene generally results in the formation of esters with low asymmetric induction.<sup>8</sup>

The reaction of ketenes  $2^9$  with chiral (S)-secondary alcohols 1 in the presence of base can result in the formation of a mixture of diastereomeric esters 3 (*RS*+*SS*) (Scheme 1).

The reaction of ketenes with (–)-menthol and (+)-borneol in the presence of various bases, resulting in low asymmetric induction, has been reported earlier.<sup>10</sup> The reaction of ketenes 2 with (S)-(+)-3-hydroxytetrahydrofuran 4 with various bases has now been carried out resulting in the formation of 5 with diastereoselectivity in the range of 8–46%.<sup>11</sup>

The reaction of ketenes 2 with (-)-menthol 1 ( $R^*$ , (-)menthyl) and (+)-borneol 1 ( $R^*$ , (+)-bornyl) in the presence of *n*-BuLi and Et<sub>2</sub>Zn results in the formation of diastereomeric esters 3 (SS+RS) with asymmetric induction in the range of 30–57% (Table 1, Scheme 1). Significant improvement in asymmetric induction catalyzed by Et<sub>2</sub>Zn was observed with (-)-menthol and (+)-borneol compared to the reaction carried out earlier with other bases.<sup>10</sup>

The reaction of (S)-(+)-3-hydroxytetrahydrofuran **4** with ketenes **2** in the presence of *n*-BuLi and Et<sub>2</sub>Zn results in the formation of ester **5** (*SS*+*SR*) with high asymmetric induction, 80–96% d.e.<sup>12</sup> (Table 2, Scheme 2). The diastereomeric excess in **5** was determined by <sup>1</sup>H NMR and <sup>13</sup>C NMR<sup>13</sup> and was found to be the same. The extent of asymmetric induction in diastereomeric esters **5** was further confirmed by hydrolysis to the optically active acids **6**. Thus, esters **5** 



Scheme 1.

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#### Table 1.

Entry	Reaction conditions	R*	$\mathbb{R}^1$	R <sup>2</sup>	Ester 3			
					Yield (%)	$[\alpha]_{\rm D}^{22}$ (acetone $c = 1.5$ )	d.e. (%) (SS>SR)	
1	<i>n</i> -BuLi Et <sub>2</sub> Zn	CH3	Me Et Me Ph	Ph Ph Cl Br	82 78 83 73	-32.5 -28.4 -22.5 -28.3	62 60 48 45	
2	<i>n</i> -BuLi Et <sub>2</sub> Zn	Me Me	Me Et Me Ph	Ph Ph Cl Br	62 59 71 63	+15.6 +12.3 +18.5 +13.4	58 49 52 48	

### Table 2.

Entry	Reaction conditions	R*OH	$\mathbb{R}^1$	$\mathbb{R}^2$	Ester 6			Acid 7	
					Yield (%)	(SS: SR)	$[\alpha]^{22}_{ m D}$	e.e. (%)	$[\alpha]^{22}_{\mathrm{D}}$
1	n-BuLi–Et <sub>2</sub> Zn	4	Me	Ph	78	98:2	+22.58	96	+69.2
2	n-BuLi–Et <sub>2</sub> Zn	4	Et	Ph	72	94:6	+16.33	84	+77.6
3	<i>n</i> -BuLi–Et <sub>2</sub> Zn	4	Br	Me	80	90:10	-9.35	80	-20.0



Scheme 2. Reagents and conditions: (a) n-BuLi/Et<sub>2</sub>Zn; (b) HCl/THF, (R<sup>1</sup>=Me, R<sup>2</sup>=Ph; (ii) R<sup>1</sup>=Et, R<sup>2</sup>=Ph; (iii) R<sup>1</sup>=Me, R<sup>2</sup>=Br.

 $(R^1 = CH_3, R^2 = Ph)$  on hydrolysis with conc. HCl in THF for 48 h at room temperature gave (*S*)-(+)-2-phenylpropanoic acid in 82% yield, e.e. 96%  $[[\alpha]_D^{22} = +69.2 \ (c=1.4, CHCl_3)]$ . The absolute configuration was assigned to the 2-phenylpropanoic acid by comparison with the specific rotation of (*S*)-(+)-enantiomer.<sup>14</sup>

The proton transfer at C2 in ketene 2 from 4 is the key and crucial step for induction of stereoselectivity. Reactions carried out in the presence of catalytic  $Et_2Zn$  lead to a high degree of diastereoselectivity, possibly due to chelation control with Zn.

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- 9. Ketenes were generated in situ from the corresponding acid chlorides and  $Et_3N$ . The pale yellow colored ketenes were used immediately for the addition reactions.
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- 11. A solution of (S)-(+)-3-hydroxy tetrahydrofuran **4** (176 mg, 2 mmol) in anhydrous toluene was prepared at  $-90^{\circ}$ C (5 mol) in dry toluene under a N<sub>2</sub> atmosphere. Ketene **2** (R<sup>1</sup>=C<sub>2</sub>H<sub>5</sub> and R<sup>2</sup>=Ph) prepared from 2-phenylbutyroyl chloride (364 mg, 2 equiv.) was added and stirred for 12 h at 0°C. Saturated brine solution (50 ml) was added and the reaction mixture extracted with ether (3×50 ml), dried (MgSO<sub>4</sub>), concentrated (in vacuo) to yield **5** (d.e. 45%). The reaction was carried out in the presence of different bases: pyridine, KO'Bu, Dabco and

DBU. The d.e. ranges are from 8-46% with the maximum d.e. obtained with Dabco and the minimum with pyridine 8%.

- 12. Reaction conditions: A solution of 4 (88 mg, 1 mmol) in dry toluene (10 ml) at  $-78^{\circ}$ C was treated with 1 ml of *n*-BuLi (2.48 M hexane solution, 1 equiv.) under a N<sub>2</sub> atmosphere. The solution was stirred for 15 min then methyl phenyl ketene 2 (i) (from 168 mg of *n*-propanonyl chloride, 1 equiv.) and 5.80 ml of Et<sub>2</sub>Zn (1 M toluene solution, 2.2 equiv.) were added. The reaction was stirred at this temperature for 1 h and then for 12 h at 0°C. Saturated brine solution (25 ml) added and extracted with ether (3×25 ml), the ether extract dried (MgSO<sub>4</sub>) and concentrated in vacuo to yield **5** as an oil which was purified by flash chromatography over Al<sub>2</sub>O<sub>3</sub> (benzene).
- 13. The structures of all the compounds were confirmed by IR, <sup>1</sup>H and <sup>13</sup>C NMR. For **5** (Table 2, entry 2) NMR data are as follows:
  <sup>1</sup>H (CDCl<sub>3</sub>, 200 MHz, δ ppm): 0.89, 0.91 (3H, 2t, *J*=7.5 Hz, CH<sub>3</sub> (4)), 1.90 (4H, m, CH<sub>2</sub>, (3,4')), 3.39, 3.41 (1H, 2t, *J*=7.5 Hz, CH (2)), 3.80 (4H, m, CH<sub>2</sub> (2', 5')), 5.25 (1H, m, CH (3')), 7.12, 7.15 (5H, 2s, Ph). Assignment of resonances. <sup>13</sup>C, <sup>1</sup>H correlations for **5** (*SS+RS*): <sup>13</sup>C (CDCl<sub>3</sub>, 100 MHz, δ ppm): C<sub>2</sub>=52.907, 52.969; C<sub>3</sub>=26.166, 26.263, C<sub>4</sub>=11.662, C'<sub>2</sub>=72.567, 72.429, C'<sub>3</sub>=74.528, 74.547, C'<sub>4</sub>=32.179, 32.441, C'<sub>5</sub>= 66.404, 66.434. The ratio of peaks at 3.39 and 3.41 for CH-2 in the <sup>1</sup>H NMR and at 52.907 and 52.969 for C<sub>2</sub> in <sup>13</sup>C NMR was used to estimate the diastereomeric excess in **5**.
- 14. An optically pure sample of (S)-(+)-2-phenylpropanoic acid from Aldrich, Milwaukee, WI, USA, had [α]<sup>20</sup>=+72 (c=1.6, CHCl<sub>3</sub>); (S)-(+)-2-phenyl butyric acid had [α]<sup>19</sup>=+92 (c=0.9, toluene) and (S)-(-)-2-bromopropionic acid had [α]<sup>20</sup>=-25 (neat).