

## Asymmetric Synthesis of $\alpha$ -Halo Esters

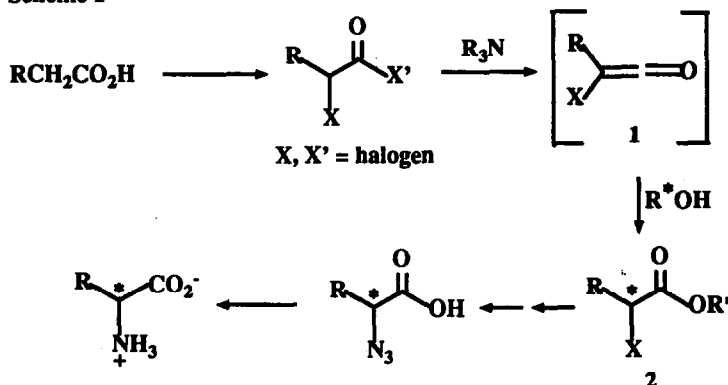
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**Abstract:** The reaction of (*R*)-Pantolactone with  $\alpha$ -halogenated ketenes has been found to proceed with good to excellent diastereoselectivities (de 75 to > 95%). The (*R*)-Pantolactone chiral auxiliary induced the (*S*)-configuration at the new chiral center in most cases.

Larson and Corley reported in 1989<sup>1</sup> that esters of 2-arylpropionic acids were obtained with diastereomeric excesses as high as 99.5% via the reaction of in-situ generated arylmethylketenes with a variety of optically active  $\alpha$ -hydroxy esters such as lactates, mandelates, tartrates and pantolactone. We rationalized that the parallel reaction of the  $\alpha$ -halogenated ketenes 1 with similar alcohols should generate the optically active  $\alpha$ -halo esters 2, which are potential precursors to the corresponding  $\alpha$ -amino acids<sup>2</sup> and other  $\alpha$ -heteroatom substituted acids.<sup>3</sup>

Scheme 1



This communication reports the realization of Scheme 1 and shows that acids of the general structure  $\text{RCH}_2\text{CO}_2\text{H}$  can be converted, with good to excellent enantiomeric excesses, into optically active  $\alpha$ -haloesters 2. At this point, (*R*)-pantolactone appears to be a superior chiral auxiliary than the other  $\alpha$ -hydroxy esters such as (*S*)-methyl lactate.

The generation of  $\alpha$ -halogenated ketenes from  $\alpha$ -halo acid halides has been reported.<sup>4-8</sup> Halogenated ketenes are fairly labile and are therefore generated in situ by the reaction of the corresponding  $\alpha$ -halo-acyl halides with a tertiary amine. A representative procedure for the preparation of  $\alpha$ -halo esters 2 is as follows: The  $\alpha$ -halo acid halide<sup>9</sup> (1-5 mmol) in dry THF (15-20 mL) was added dropwise to a solution of (*R*)-pantolactone and dimethylethylamine (2 eq each, 0.2 M in THF at  $-78^\circ\text{C}$ ) over a period of one hour. The reaction mixture was then removed from the cold bath and stirred at room temperature for 15 minutes (at which time the temperature of the reaction mixture rose to  $10^\circ\text{C}$ ) or allowed to warm to room temperature slowly over the indicated period of time (see Table 1). The mixture was quenched with water and subjected to extractive

workup. The diastereomeric ratio was then determined from the  $^1\text{H}$  NMR of the crude reaction mixture in  $\text{CDCl}_3$  or  $\text{C}_6\text{D}_6$ . Signals which arose from the proton H-2 or H-2' were most useful in the diastereomeric ratio determination.

From the list of substrates investigated, the reaction has been found to proceed with good to excellent diastereoselectivities giving the expected  $\alpha$ -halo esters (Table 1).<sup>10</sup> The reaction appears to be applicable to substrates with a wide variety of structures.<sup>11</sup>

Table 1. Synthesis of  $\alpha$ -halo-esters

Entries	R	X	X'	Ratio of diastereomers major : minor	% de	Warming period (hrs)	% Yield <sup>a</sup>
1	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	Br	Cl	14 : 1	87	20	79
2	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Br	Cl	8 : 1	78	0.25	78
3	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	I	Cl	12 : 1	85	4.5	71
4	<i>c</i> -C <sub>5</sub> H <sub>9</sub>	I	Cl	19 : 1	91	4.5	73
5	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	I	Cl	15 : 1	88	0.25	51
6	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CH	I	Cl	single isomer	> 95	4.5	52
7	<i>c</i> -C <sub>6</sub> H <sub>11</sub> CH <sub>2</sub>	I	Cl	7 : 1	75	0.25	48
8	<i>n</i> -C <sub>2</sub> H <sub>5</sub>	Br	Br	11 : 1	83	0.25	84
9	<i>n</i> -C <sub>2</sub> H <sub>5</sub>	Br	Cl	7 : 1	75	0.25	63

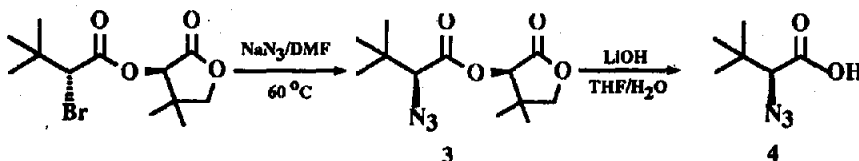
<sup>a</sup> Total yield of both isomers isolated by chromatography on silica gel (10% EtOAc/Hexanes as eluent)

The rapid warming of the reaction mixture described above in entries 2, 5, and 7-9 is absolutely essential for obtaining products of high optical purity. Products obtained from slow warming (for example 4 hours) showed considerable loss of stereochemical integrity at the newly created chiral center presumably due to epimerization caused by the excess base.<sup>12</sup> Reaction of the sterically hindered *t*-butyl- $\alpha$ -bromoketene (entry 1) with pantolactone required a much longer reaction time. A shorter reaction time (for example 4 hours) resulted in a lower yield (30 %) of the ester 2. The sterically hindered esters 2 obtained in this case is not susceptible to base epimerization. The choice of halogen (X or X') in the substrates also appears to be important for achieving high diastereoselectivity in the reaction. The  $\alpha$ -iodo acid chloride gave higher selectivity when compared to the corresponding  $\alpha$ -bromo acid chloride (entries 3 vs 2). The higher selectivity observed in this case could be due to the fact that the resulting chiral  $\alpha$ -iodo esters 2 are less susceptible to base epimerization than their bromo counterparts. Acid bromides also appear to react with higher selectivity when compared to the corresponding acid chloride (entries 8 vs 9). The later observation is likely due to the fact that acid bromides form ketenes more efficiently than the corresponding acid chloride.<sup>13</sup> The formation of ketene is essential for the diastereoselectivity of the reaction. Direct reaction of  $\alpha$ -halo acid halides with the chiral alcohol in the absence

of dimethylethylamine gave the expected ester **2** but with no diastereoselectivity.

The absolute stereochemistry of the  $\alpha$ -halo esters was established as follows: The  $\alpha$ -halo ester from the reaction of *t*-butyl- $\alpha$ -bromoketene (entry 1, 14:1 mixture) was treated with LiOH (2 eq, THF/H<sub>2</sub>O (2:1), 20 hrs at 24 °C) to give the known 2-bromo-3,3-dimethylbutanoic acid (70%,  $[\alpha]_D^{28}$  -10.65° (c 2.40, MeOH), 88.7% ee, lit.<sup>14</sup>  $[\alpha]_D^{27}$  + 12.0° (MeOH) for the *S* antipode) with the *R* configuration. However, hydrolysis of the  $\alpha$ -halo ester from the reaction of 2-bromobutanoyl bromide (entry 8, 11:1 mixture, THF/H<sub>2</sub>O (2:1), LiOH (1.5 eq), 25 mins at 3 °C) gives the known 2-bromobutanoic acid (75 %,  $[\alpha]_D^{28}$  -24.5° (c 1.51, MeOH), 77% ee, lit.<sup>14</sup>  $[\alpha]_D^{27}$  -31.7° (MeOH) for the (*S*) antipode) with the *S* configuration. In view of the discrepancies in the stereochemistries observed, the ester from the reaction of 2-bromo-3-methylbutanoyl chloride (entry 2, 8:1 mixture) was also hydrolysed (THF/H<sub>2</sub>O (2:1), LiOH (1.5 eq), 1 h at 24 °C) to give the known 2-bromo-3-methylbutanoic acid (65 %,  $[\alpha]_D^{28}$  -11.0° (c 1.10, MeOH), 65% ee, lit.<sup>14</sup>  $[\alpha]_D^{27}$  -16.8° (MeOH) for the (*S*) antipode) with the *S* configuration. It would appear that *t*-butyl- $\alpha$ -bromoketene is a unique case showing opposite stereochemistry. The other substrates studied are assumed to have produced esters with the *S* configuration at the new chiral center, based on their structural similarity to substrates in entries 2 or 8. The chiralities observed for the substrates in entries 2 and 8 are consistent with those reported for non-halogenated ketenes.<sup>1</sup>

To examine the conversion of  $\alpha$ -halo esters **2** to the corresponding  $\alpha$ -amino acids, the product from the reaction of *t*-butyl- $\alpha$ -bromoketene (entry 1, 14:1 mixture) was chosen as a representative case. Treatment of the ester with NaN<sub>3</sub> in DMF (5 eq at 60 °C for 40 hrs) gave the expected azido ester **3** with inversion of configuration. Azide displacement under the stated condition is known to proceed with inversion of configuration and slight epimerization (approx 10%).<sup>2</sup> The faster running minor azide epimer could be partially removed by flash chromatography, giving the ester **3** as a 7:1 mixture (70%). The azido ester was then saponified (LiOH (1.5 eq), THF/H<sub>2</sub>O, 18 hrs at 24 °C) to give the known (*S*)- $\alpha$ -azido-3,3-dimethyl butanoic acid **4**<sup>15</sup> (70% after chromatography (hexanes/EtOAc/AcOH 5:1:0.2),  $[\alpha]_D^{24}$  -51.7° (c 1.43, CHCl<sub>3</sub>), 72% ee, lit.<sup>16</sup>  $[\alpha]_D^{24}$  -71.6° (c 4.06, CHCl<sub>3</sub>) for the (*S*) antipode). The conversion of azido acid **4** to the corresponding  $\alpha$ -amino acid has been reported.<sup>16</sup>



In conclusion, the reaction of  $\alpha$ -halogenated ketenes has been found to proceed with good to excellent diastereoselectivities. The reaction could be applied to substrates with widely different structures with the exception of the  $\alpha$ -arylated- $\alpha$ -halogenated ketenes.<sup>11</sup> The chiral alcohol (*R*)-pantolactone induces the *S* stereochemistry in most cases. We are currently investigating the reaction of ketenes bearing other  $\alpha$ -substituent (eg.  $\alpha$ -azido,  $\alpha$ -alkoxy and  $\alpha$ -thio ether) with various chiral alcohols.

#### Acknowledgments

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## References and Notes

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