Pergamon

*Tetrahedron Letters*, Vol. 37, No. 16, pp. 2683-2686, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00391-7

# Stereoselective Synthesis of 2-Aryloxy Acids from Lactamide Derived Esters of Racemic α-Halo Carboxylic Acids.

Paul N. Devine,* Ulf -H. Dolling, Richard M. Heid, Jr., David M. Tschaen
Department of Process Research, Merck Research Laboratories
Division of Merck & Co., Inc.
P.O. Box 2000, Rahway, New Jersey 07065, USA

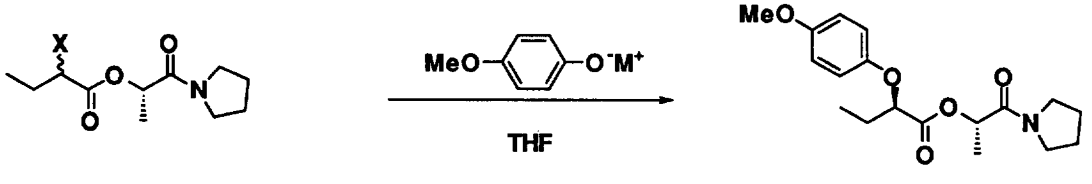
*Abstract: Pyrrolidine derived (S)-lactamide auxiliaries mediate a highly stereoselective coupling reaction between racemic α-haloacids and aryloxides. These amide auxiliaries exhibit enhanced rates of reaction as well as increased degrees of diastereoselection over conventional ester auxiliaries.* Copyright © 1996 Elsevier Science Ltd

During the course of our studies directed towards the asymmetric synthesis of a potent endothelin antagonist, we had need for a highly stereoselective synthesis of 2-aryloxy carboxylic acids. A variety of methods have been developed to meet this goal with results of general applicability being obtained by Durst and Koh utilizing (R)-pantolactone as a chiral auxiliary.[1] Pantolactone esters of racemic α-halo acids have been coupled via an $S_N2$ reaction to a variety of phenoxides. Diastereoselectivities ranging from 76-90% have been obtained in this fashion with the "S" stereochemistry predominating at the newly formed asymmetric center. The "R" stereochemistry can be obtained utilizing (S)-ethyl lactate as the chiral auxiliary although diastereoselectivities are significantly lowered in comparison to pantolactone (60-75%).[2] The reaction is also characterized by sluggish rates and moderate yields. Durst has invoked a mechanism involving a halide to halide transposition reaction to account for the observed diastereoselectivity of the reaction.[1b] Presumably, significant differences in rates of reaction exist between the two diastereomeric halides. This allows for epimerization of the slower reacting α-halo ester into the faster reacting isomer by halide generated throughout the reaction. This process is accelerated through the addition of extraneous iodide to the reaction mixture and reactions were typically conducted in the presence of 20 mol% of a tetraalkylammonium iodide salt. Herein we wish to describe a highly stereoselective coupling reaction mediated with a pyrrolidine derived lactamide auxiliary. The auxiliary is readily available in one step from (S)-ethyl lactate and diastereoselectivities greater than 90% are routinely obtained.

The auxiliary is synthesized from (S)-ethyl lactate under Weinreb amidation conditions employing trimethylaluminum and pyrrolidine.[3] The reaction is complete in less than 2h with no detectable loss in the enantiopurity. The product is obtained in 80% yield with the lactamide formed being suitable for use without further purification. Alternatively, the auxiliary can be synthesized by stirring ethyl lactate with a slight excess of pyrrolidine neat.[4] The reaction is complete in 72 h and product is distilled directly from the reaction in 95% yield. The lactamide esters of the racemic α-halo acids were prepared via DCC coupling with commercially available acids or upon reaction with commercially available acid halides according to literature procedure.[5]

The coupling reaction was conducted by adding a preformed solution of aryloxide to a THF solution of halide, with or without tricaprylmethylammonium iodide, at the desired temperature (Table **1**).[6] The reactions with the lactamide auxiliary were found to proceed at a much faster rate than with ester auxiliaries. A reaction performed at -35°C with sodium 4-methoxyphenoxide was completed in 0.5h with a diastereoselectivity of 92% (entry **1**).

**Table 1**



1

2

| Entry | Temp (°C) | Metal | X | Time (h) | Yield(%) | DR** |
|---|---|---|---|---|---|---|
| 1 | -35 | Na | Br | 0.5 | 78 | 96:4 |
| 2* | -35 | Na | Br | 0.5 | 84 | 95:5 |
| 3 | RT | Li | Br | 6 | 83 | 94:6 |
| 4 | 0 | Li | Br | 8 | 80 | 95:5 |
| 5 | -15 | Li | Br | 24 | 82 | 95:5 |
| 6* | RT | Li | Br | 6 | 79 | 95:5 |
| 7* | 0 | Li | Br | 8 | 83 | 95:5 |
| 8* | -15 | Li | Br | 24 | 86 | 96:4 |
| 9 | RT | Li | I | 0.25 | 87 | 98:2 |
| 10 | 0 | Li | I | 0.5 | 89 | 99:1 |

* Reaction conducted in the presence of 20mol% tricaprylmethylammonium iodide. ** Diastereoselectivities determined via HPLC utilizing a Chiracel OD column and via 300MHz $^1$H NMR integration of the diastereomeric methyl doublets.

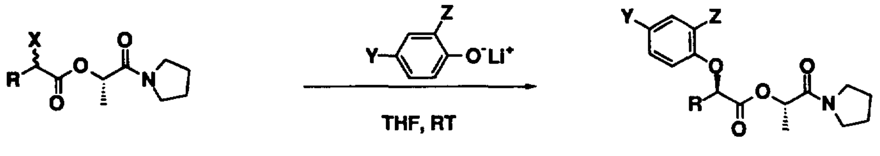
By comparison, a reaction utilizing ethyl lactate as the auxiliary required a reaction time of 24h at 0°C and the product was also obtained with a diminished diastereoselectivity of 60%. No improvement in diastereoselection was observed upon running the reaction in the presence of 20 mol% tricaprylmethylammonium iodide with the lactamide auxiliary (entry **2**). This observation also holds true for the ethyl lactate auxiliary. This indicates that a halide to halide transposition reaction takes place between the sodium bromide formed in the reaction and the slower reacting (2R)-bromoester or that the reaction is operating via an alternative mechanism to that proposed by Durst.[1]

The fact that coupling reactions involving pyrrolidine lactamide auxiliaries proceed at a more rapid rate than their ester counterparts allows for the use of alternative phenoxide salts. Lithium 4-methoxyphenoxide reacts sluggishly at -35°C, but readily undergoes reaction with the α-bromoester at temperatures ranging from -15°C to ambient (entries **3-5**). Lithium phenoxides proved to be unreactive towards ester auxiliaries under these conditions.

The effect of temperature was found to be negligible, with diastereoselectivities obtained at room temperature rivaling those obtained at -35°C. Once again, the effect of 20 mol% added iodide was negligible (entries **6**-**8**). However, conducting the coupling reaction utilizing the α-iodoester leads to significant increases in diastereoselection (entries **9** & **10**).[7] Reactions performed at ambient temperature and 0°C showed enhanced diastereomeric ratios of 98:2 and 99:1 respectively.

The generality of the reaction was expanded by studying a variety of diastereomeric halides and substituted phenols (Table **2**).

**Table 2**



**3** **4**

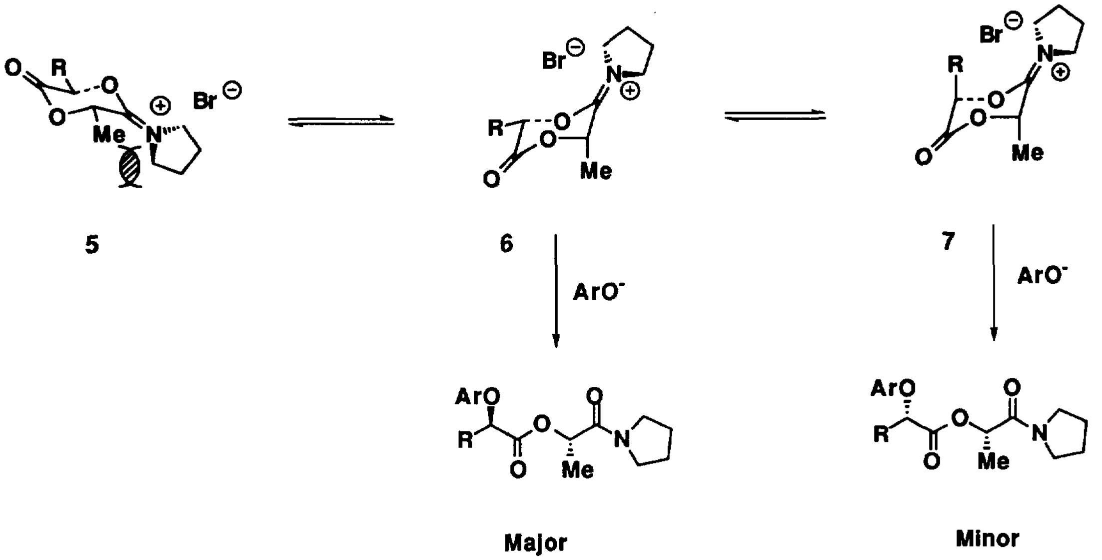
| Entry | R | X | Y | Z | Time(h) | Yield(%) | DR* |
|---|---|---|---|---|---|---|---|
| 1 | Et | Br | H | nPr | 3 | 76 | 95:5 |
| 2 | Ph | Br | H | H | 0.75 | 78 | 97:3 |
| 3 | Ph | Br | H | nPr | 0.50 | 77 | 96:4 |
| 4 | Ph | Br | OMe | H | 0.25 | 88 | 98:2 |
| 5 | Ph | I | OMe | H | 0.10 | 87 | 99:1 |

* Diastereomeric ratio determined via HPLC utilizing either a Supelcosil LC CN column or a Chiracel OD column. Diastereoselectivities could also be obtained via 300MHz $^1$H NMR.

The substitution pattern about the phenols utilized had minimal influence on the diastereoselectivity of the reaction. The more sterically demanding 2-propylphenol gave similar diastereomeric ratios to unencumbered phenols (entries **1**, **2**-**4**). Again, diastereoselectivities observed are on the order of 5-15% higher than those obtained utilizing either ethyl lactate or pantolactone as the chiral auxiliary. Diastereomeric ratios of 99:1 can be obtained at room temperature through utilization of the α-iodoester (entry **5**). The reaction is complete upon addition of the phenoxide and excellent yields are obtained.

The absolute configuration of the newly formed stereogenic center was determined to be "R" by converting the coupled product from entry **5** to methyl mandelate.[8] The product was treated with LiOOH giving the acid with no detectable racemization. The auxiliary was recovered in 91% yield further adding to the synthetic utility of this reaction. The acid was protected as its methyl ester and the *p*-methoxyphenyl function was then oxidatively removed via ceric ammonium nitrate affording (R)-methyl mandelate as evidenced by the large negative rotation. The ease in which the *p*-methoxyphenyl group is removed further adds to the synthetic utility of the coupling reaction by providing for the synthesis of α-hydroxy esters and acids of high optical purity.[9]

Efforts are now focused on elucidating the mechanism of this highly diastereoselective coupling reaction. We postulate that the reaction is proceeding through a cyclic transition state (Scheme **1**). Such a mechanism would account for the vast increase in rate of reaction and the high degree of diastereoselection observed in the reaction. The mechanism by which **6** and **7** interconvert is still unclear.



Scheme **1**

We are currently investigating the use of other nucleophiles such as amines and cuprates. These results and mechanistic details of the reaction will be reported in due course.

## References and Notes:

1. (a) Koh, K.; Durst, T. *J. Org. Chem.* **1994**, *59*, 4683. (b) Koh, K.; Ben, R.N.; Durst, T. *Tetrahedron Lett.* **1993**, *34*, 4473.

2. For other diastereoselective reactions utilizing pantolactone or ethyl lactate see: (a) Larsen, R.D.; Corley, E.G.; Davis, P.; Reider, P.J.; Grabowski, E.J.J. *J. Am. Chem. Soc.* **1989**, *111*, 7650. (b) Koh, K.; Ben, R.N.; Durst, T. *Tetrahedron Lett.* **1994**, *35*, 375.

3. (a) Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Basha, A.; Lipton, M.; Weinreb, S.M. *Tetrahedron Lett.* **1977**, *28*, 4171.

4. Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767.

5. (a) Durst, T.; Koh, K. *Tetrahedron Lett.* **1992**, *33*, 6799. (b) Harpp, D.N.; Bao, L.Q.; Black, C.J.; Gleason, J.G.; Smith, R.A.; *J. Org. Chem.* **1975**, *40*, 3420.

6. All new compounds described in this article displayed satisfactory analytical data.

7. The α-iodoester was prepared by treating the α-bromoester with NaI in acetone.

8. Corey, E.J.; Link, J.O. *Tetrahedron Lett.* **1992**, *33*, 3431.

9. For other asymmetric syntheses of α-hydroxy acids and esters see: (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, **1983**; Chapter 2. (b) Singh, V.K. *Synthesis* **1992**, 605.

(*Received in USA* 18 *December* 1995; *revised* 19 *February* 1996; *accepted* 21 *February* 1996)