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Synthesis of Chiral 3-Substituted Isoxazolidines.

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Abstract: The synthesis of chiral (>98% ee) 3-substituted isoxazolidines has been achieved. Glycidyl tosylate was utilized to establish the desired stereochemistry in a "double grignard" reaction sequence. Mesylate displacement followed by acid-catalyzed cyclization allows the parent isoxazolidines to be obtained. © 1997 Elsevier Science Ltd. All rights reserved.

The use of chiral auxiliaries is a valuable tool in the pursuit of complex natural products. Evans' oxazolidinones,¹ Oppolzers' sultams,² Meyers' oxazolines³ and others⁴ have been developed for asymmetric synthesis. We were interested in obtaining a new set of chiral auxiliaries which would offer greater versatility in their application as well being readily obtained. Chiral 3-substituted isoxazolidines (Scheme 1) were synthesized for several reasons: they are effectively a "chiral Weinreb" equivalent,⁵ are readily acylated, and they are crystalline solids. Masamune and coworkers have reported benzopyranoisoxazolidines⁶ and bicyclic-isoxazolidines as chiral auxiliaries.⁷



In order to obtain the desired auxiliaries, we developed a two-pronged synthetic approach. Our original efforts relied upon a [3+2] cycloaddition of nitrile oxides with olefins⁸ with subsequent enantiospecific reduction of the isoxazolines. While the parent isoxazolines (3) were obtained in good yield (51-76% overall),⁹ the subsequent hydrogenation was problematic. Modest enantiomeric excess and competing N-O bond scission¹⁰ prompted us to develop a more conventional approach.

Glycidyl tosylate (6, either enantiomer) was incorporated into a "double-Grignard" reaction sequence (Scheme 2) to obtain the isoxazolidines. For example, 4-(phenyl)-phenyl magnesium bromide was prepared and allowed to react with glycidyl tosylate¹¹ to afford 7. Stepwise treatment with potassium ethoxide and isopropenyl magnesium bromide afforded homo-allylic alcohol 8 via crystallization (96% assay, 85% isolated). Mesylation followed by nucleophilic displacement by hydroxylamine resulted in the isolation of 9 in 53% yield. Hydroxylamine 9 was then treated with triflic acid in methylene chloride to afford the desired isoxazolidine (4) in 78% yield. Acylation under Schotten-Baumann conditions was essentially instantaneous and quantitative for a variety of acid chlorides.



To date, we have developed a practical synthesis of chiral 3-substituted isoxazolidines. Isoxazolidine 4 is a crystalline solid (m.p. $104^{\circ}-105^{\circ}$ C) with λ_{max} at 254 nm. Detection with a standard UV lamp is therefore unmistakable. Amide 1 (R₁= Me) will be evaluated in a series of specific asymmetric transformations.

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- Starting materials were prepared from the corresponding aldehydes via condensation with nitromethane/borohydride reduction or oxime formation/chlorination Reported yields are from the aldehyde via a through process.
- 10. Reductions with Noyori or Burke catalysts were either slow or led to N-O bond scission. "OAB" based catalysts led to 40-60% ee (40-62% yield). See: Didier, E.; Loubinoux, B.; Ramos Tombo, G.M.; Rihs, G. *Tetrahedron* 1991, 47, 4941.
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