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Synthesis of Chiral 3-Substituted Isoxazolidines.

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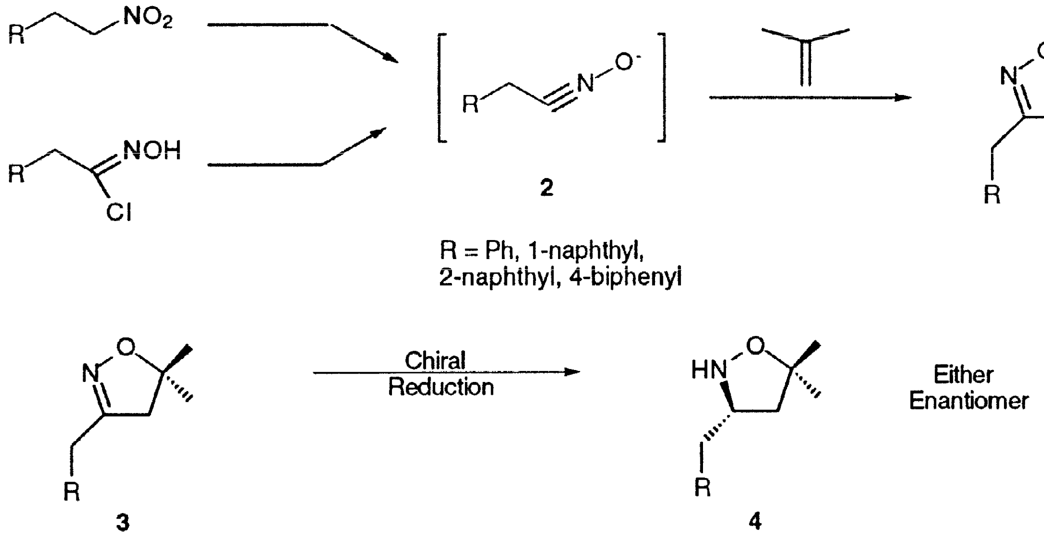
Abstract: The synthesis of chiral (>98% ee) 3-substituted isoxazolidines has been achieved. Glycidyl tosylate was utilized to establish the desired stereochemistry in a "double grignard" reaction sequence. Mesylate displacement followed by acid-catalyzed cyclization allows the parent isoxazolidines to 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' oxazolines[3] and others[4] 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 benzopyranoisoxazolidines[6] and bicyclic-isoxazolidines as chiral auxiliaries.[7]



Scheme 1

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 olefins[8] 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 scission[10] prompted us to develop a more conventional approach.

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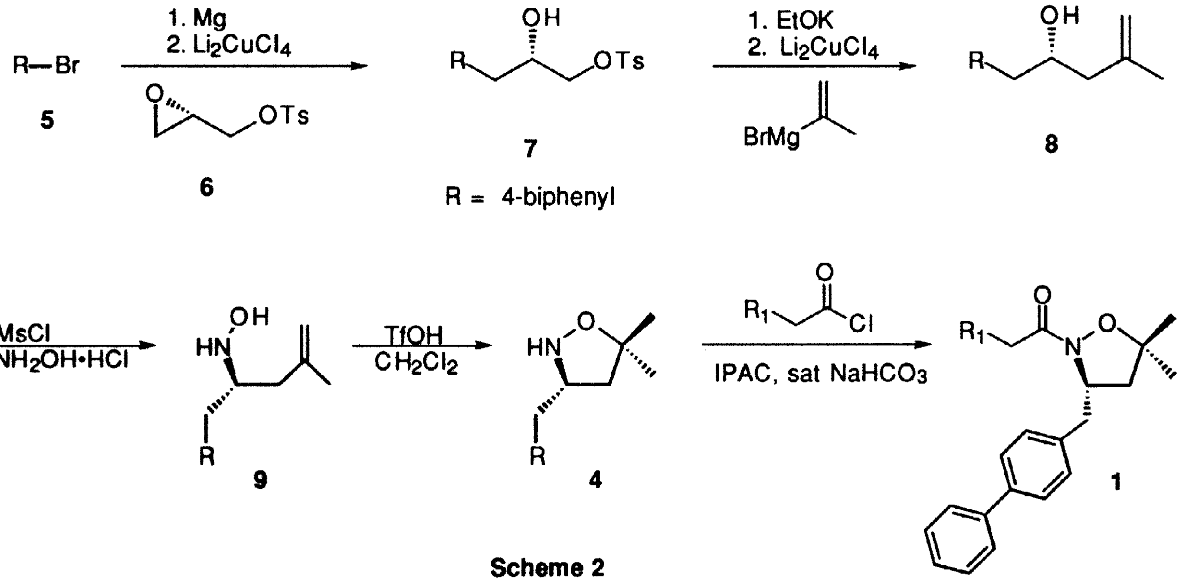
Glycidyl tosylate (**6**, either enantiomer) was incorporated into a "double-Grignard" reaction sequence (Scheme 2) to obtain the isoxazolidines. For example, 4-(phenyl)-phenyl magnesium bromide was prepared and allowed to react with glycidyl tosylate[11] to afford **7**. Stepwise treatment with potassium 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.



Scheme 2

To date, we have developed a practical synthesis of chiral 3-substituted isoxazolidines. Isoxazolidine **4** is a crystalline solid (m.p. 104°-105°C) with λ_{max} at 254 nm. Detection with a standard UV lamp is therefore unmistakable. Amide **1** (R_1= Me) will be evaluated in a series of specific asymmetric transformations.

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9. 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.
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