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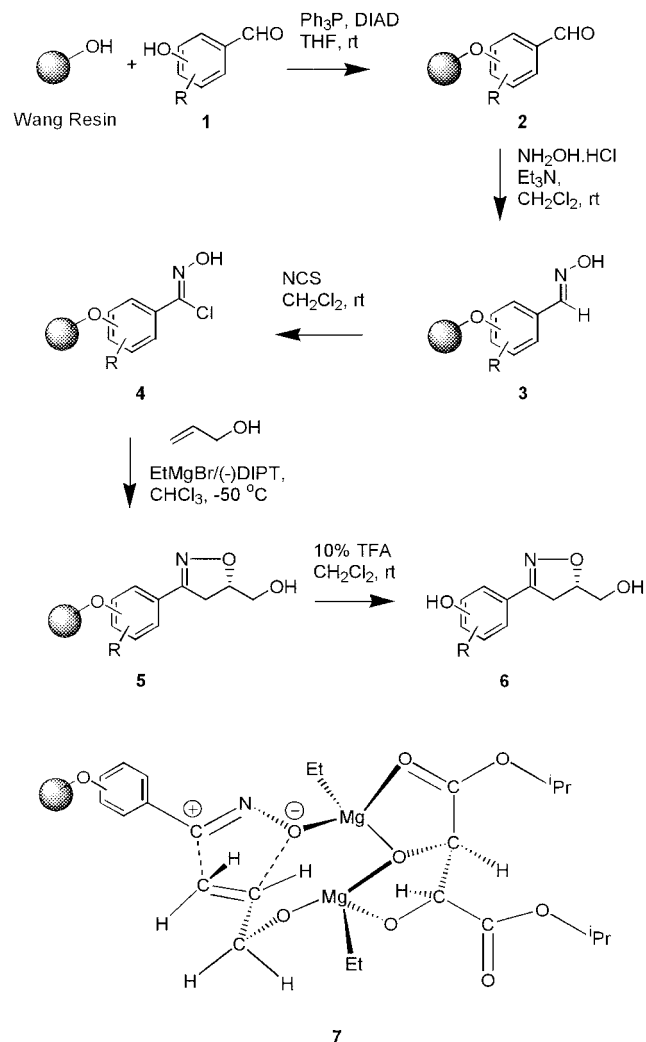
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The solid phase synthesis of combinatorial chemistry has changed the way in which drug discovery is conducted in the pharmaceutical industry.¹ A number of recently reported pharmaceutically active agents, such as glycoprotein IIb/IIIa receptor antagonists² and human leukocyte elastase inhibitors,³ contained an optical isoxazoline ring, which played an important role in their biological activities. 1,3-Dipolar cycloaddition between nitrile oxide and alkene is the most useful convenient method for the preparation of isoxazoline derivatives. Besides being potential pharmaceutical agents, the isoxazolines have found numerous applications in synthesis through reductive cleavage of the N–O bond to give 1,3-amino alcohol.⁴ A lot of enantioselective syntheses of isoxazolines in solution phase have already been studied through incorporation of chirality in both the dipole and dipolarophile or coordination of metal/dipole/dipolarophile with chiral auxiliary.⁵ However, solid phase asymmetric 1,3-dipolar cycloaddition remains unexplored.⁶ In this paper, we describe an enantioselective 1,3-dipolar cycloaddition in solid phase using (–)-diisopropyl tartrate ((–)-DIPT) as auxiliary and Grignard reagent as base.

Resin-bound aldoxime was prepared according to Scheme 1. The substituted hydroxyl benzaldehyde **1** was attached to Wang resin by Mistunobu reaction. The resin-bound benzaldehyde **2** was then treated with hydroxylamine hydrochloride in the presence of triethylamine to give resin-bound aldoxime **3**. Reaction of aldoxime resin **3** with *N*-chlorosuccinimide in methylene chloride afforded the chlorooxime resin **4**. It was reported that a stoichiometric amount of (+)-diisopropyl tartrate-diethyl zinc reagent induced an asymmetric 1,3-dipolar cycloaddition of nitrile oxide with allylic alcohol in solution phase.⁷ Initially, a solid phase asymmetric 1,3-dipolar cycloaddition reaction was carried out according to Ukaji's solution phase procedure using diethyl zinc as base.⁷ However, only racemic isoxazoline **6a** was obtained in a yield of 38% (Table 1, entry 1). After many trials, the solid phase asymmetric 1,3-dipolar cycloaddition of a resin-

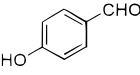
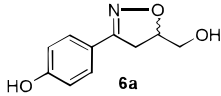
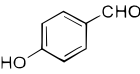
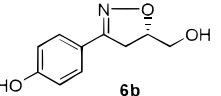
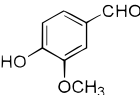
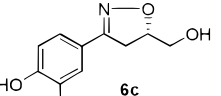
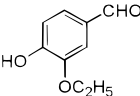
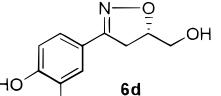
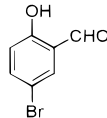
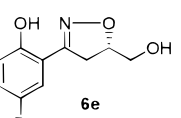
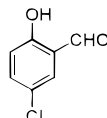
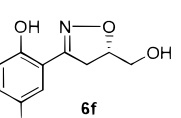
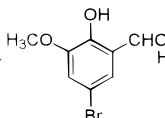
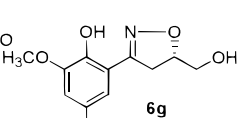
Scheme 1



bound aromatic nitrile oxide was successfully achieved by using EtMgBr as base and (–)-diisopropyl tartrate as chiral auxiliary (Table 1, Scheme 1). Thus, allylic alcohol was treated with EtMgBr at –50 °C. Then, to this was added (–)-DIPT and a second portion of EtMgBr. The mixture was transferred into resin-bound chlorooxime **4** in chloroform and shaken overnight. Cleavage from the resin with dilute TFA in dichloromethane gave isoxazoline **6** with good regioselectivity and enantioselectivity in approximately 63–78% yield with ee of 62% up to 95% (entries 2–7). The substituted groups in the aromatic ring did not obviously affect the stereoselectivity of the reaction. The absolute configurations of the isoxazoline were assigned to be *S* by comparison of the positive specific rotation of **6b** (entry 2) with the reported data for its *R*-enantiomer which has negative specific rotation. The mechanism of the solid phase

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Table 1. Asymmetric 1,3-Dipolar Cycloaddition of Resin-Bound Aromatic Nitrile Oxide to Allylic Alcohol Using (*S,S*)-(-)-DIPT as Auxiliary

| entry | benzaldehyde 1 | isoxazoline 6 | ee (%) ^a | yield (%) ^c | crude purity (%) |
|-------|---|---|---------------------|------------------------|------------------|
| 1 |  |  | 0 ^b | 38 | 50 |
| 2 |  |  | 81 | 70 | 80 |
| 3 |  |  | 73 | 69 | 78 |
| 4 |  |  | 62 | 63 | 81 |
| 5 |  |  | 65 | 78 | 90 |
| 6 |  |  | 80 | 71 | 83 |
| 7 |  |  | 95 | 75 | 75 |

^a Optical yields were determined by HPLC analysis (Daicel Chiralcel OD, Chiralcel OJ, or Chiralpak AD). ^b ZnEt₂ was used as base. ^c Crude overall yield for five steps.

asymmetric 1,3-dipolar cycloaddition was assumed to be the same as its solution phase reaction using Et₂Zn as base.⁷ The bimetallic chelation transition state **7** arising from the coordination of 1,3-dipole resin-bound aromatic nitrile oxide, dipolarophile allylic alcohol, and (-)-DIPT on magnesium ions should be responsible for the enantioselective cycloaddition.

In summary, a facile method for the asymmetric solid phase synthesis of isoxazolines has been developed. It involved the use of (-)-DIPT as auxiliary and EtMgBr as base. The solid phase asymmetric 1,3-dipolar cycloaddition is useful for building a library of optical isoxazolines for pharmaceutical drug discovery.

Supporting Information Available. General experimental procedures and characterization data for isoxazolines are available free of charge via the Internet at <http://pubs.acs.org>.

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