

DOCTORAL THESIS

1,3-dipolar cycloadditions of α , β -unsaturated sultone and sultams

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**1,3-Dipolar Cycloadditions of
 α,β -Unsaturated Sultone and Sultams**

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**A thesis submitted in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy**

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Abstract

The use of 1-propene-1,3-sultone (**2-1**) as a new dipolarophile in 1,3-dipolar cycloaddition reaction was explored. Achiral nitrones reacted smoothly with **2-1** in refluxing toluene for 12-24 h to give bicyclic isoxazolidines **2-10a-g** with high chemical yields and remarkably high degree of regio- and *endo*-selectivity. The corresponding asymmetric 1,3-dipolar cycloaddition reaction of chiral nitrones with **2-1** have also been examined. Chiral nitrones **2-11a-e** underwent the 1,3-dipolar cycloaddition reaction with **2-1** in toluene at 90 °C for 24-36 h, giving adducts with high diastereoselectivity up to 5.1:1.

A number of nitrile oxides (**3-9a-f**) were *in situ* generated by Huisgen's method and their subsequent cycloaddition with **2-1** in toluene at room temperature for 12 –24 h to afford bicyclic 2-isoxazolines in high isolated yields with complete regio- and *endo*-selectivities. Also, the asymmetric version of the cycloaddition between chiral nitrile oxides and **2-1** were studied. The clean reaction gave 50 % yield of the optically active adduct with diastereomeric ratio of 1.5:1.

To further explore the chemistry of the 1,3-dipolar cycloaddition reaction, the scope of the asymmetric reaction of chiral unsaturated sultam **4-4** with nitrile oxides **4-6a-e** and nitrones **4-13a-d** was investigated. In most of the cases, irrespective of the nature of the dipoles, only very marginal diastereoselectivity was observed for the 1,3-dipolar cycloaddition reaction. In contrast, using double asymmetric induction strategy, the cycloaddition products from sultam **4-4** and chiral nitrone **4-13d** was obtained in the best diastereoselectivity ratio of 7.1:1.

To prepare useful synthetic materials, further transformations of the cycloadducts were undertaken. The reductive N-O bond cleavage on the isoxazolidine derivatives **5-1a-g** under atmospheric pressure at room temperature with Raney nickel provided the corresponding 1,3-amino alcohols **5-2a-g** in about 80 % yield. More efficient preparation of the ring-opening products with 90 % yield and 100% conversion was achieved when hydrogenation was carried out under a pressure of 40 psi in the presence of triethylamine. On the other hand, to follow the established four-step protocol, cycloadducts from the 1,3-dipolar cycloaddition reaction were converted into a series of chiral bicyclic sultams **5-6** and **5-7**, which were used as new chiral auxiliaries. *N*-Enoyl sultams **5-10** and **5-11** were prepared *via N*-acryloylation of the sultams, and their asymmetric Diels-Alder reactions were studied. The *N*-enoyl bicyclic sultams underwent smooth reactions with excess cyclopentadiene in the presence of TiCl₄ to afford cycloadducts with excellent chemical yields and very high diastereoselectivity. The effects of Lewis acids, reaction temperature and the structures of bicyclic sultams on the cycloaddition were examined. There was no significant difference between TiCl₄ and SnCl₄ in their catalytic properties to promote the reaction. Increasing the reaction temperature from -78 °C to -50 °C, *N*-enoyl sultams reacted in a faster rate with cyclopentadiene but at the expense of the diastereoselectivity. Regarding to the chiral induction ability, chiral auxiliaries **5-7** containing isoxazolidine moiety are superior to those of the isoxazoline derivatives **5-6**. *N*-Crotonyl sultams exhibited higher asymmetric induction than *N*-acryloyl derivatives for both isoxazolidine and isoxazoline chiral auxiliaries. Reasonable transition states have been proposed for explaining the

stereochemical outcome of the reaction.

Finally, some multifunctional isoxazolidine derivatives were used for the design of fluorescent sensors for metal ion determination. Adduct **5-1e** possessing a pyrenyl group has been developed as a new fluorescent sensor for detecting Ag^+ with remarkable high selectivity and sensitivity.

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