

## DOCTORAL THESIS

### Chiral $\beta$ -amino sulfoxides and chiral sultams in asymmetric synthesis

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**Chiral  $\beta$ -Amino Sulfoxides and Chiral Sultams  
in Asymmetric Synthesis**

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## Abstract

In an attempt to develop new chiral catalysts in the asymmetric addition of diethylzinc with benzaldehyde, a series of  $\beta$ -aminosulfoxides possessing isoquinoline and  $\beta$ -carboline skeletons have been synthesized and characterized. Experimental results revealed that these ligands only demonstrated a marginal catalytic property for the addition reaction, indicating that ligands possessing a sulfinyl group and a basic nitrogen in a cyclic secondary or tertiary amine form are not efficient in catalyzing this addition reaction in an enantioselective manner.

The use of the rational chemically designed norbornenesultam, (-)-(1*S*, 2*R*, 6*R*, 7*R*)-3,4-thiazatricyclo [5.2.1.0<sup>2,6</sup>] deca-8-ene-3,3-dioxide, and its antipode as highly practical chiral auxiliaries for asymmetric alkylation and aldol reactions have been developed.

Norbornenesultam can be synthesized from allyl bromide through a five-step reaction sequence with 34% overall yield. Due to the high crystallizability of the auxiliary moiety, most of the products of alkylation and aldolization are frequently crystalline and are easily enriched to high enantiomeric purity upon recrystallization.

The chiral auxiliaries undergo efficient and highly diastereoselective alkylation reactions with a wide range of halides including less reactive substrates such as *n*-alkyl halides. Diastereoselectivities of up to 94% de can be routinely achieved. It is particularly noteworthy that *N*-acylnorbornenesultam can react with racemic ethyl  $\alpha$ -bromopropanoate,  $\alpha$ -bromobutanonate, and  $\alpha$ -bromohexanoate in a highly stereoselective manner. Among the four possible products, only one diastereoisomer was isolated. Under the experimental conditions, not only was the absolute configuration of the  $\alpha$ -carbon of the acyl group completely controlled, but also the stereochemical control was further

extended to the  $\beta$ -carbon. The absolute configurations generated in the alkylations were unambiguously established by X-ray studies.

Further transformations of the products of the asymmetric alkylation reaction were also investigated. Non-destructive cleavage reactions of the alkylated products provided direct access to highly enantiomerically enriched carboxylic acids, esters and alcohols. In addition, using the alkylated products as starting materials, a new methodology for an efficient synthesis of a variety of chiral 1,3-di-, and 1,3,4-trisubstituted pyrrolidines was developed. The synthesis of two naturally occurring 1,3-disubstituted pyrrolidines was achieved *via* the newly developed route for the first time.

$\text{TiCl}_4$  promoted the aldol condensations of the derived *N*-acylated norbornenesultam with aromatic and aliphatic aldehydes afforded *anti* aldol products with high diastereoselectivities. The effects of the structure of the chiral auxiliaries and aldehydes were also examined.

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