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Glyoxylic acid derivatives in asymmetric synthesis*

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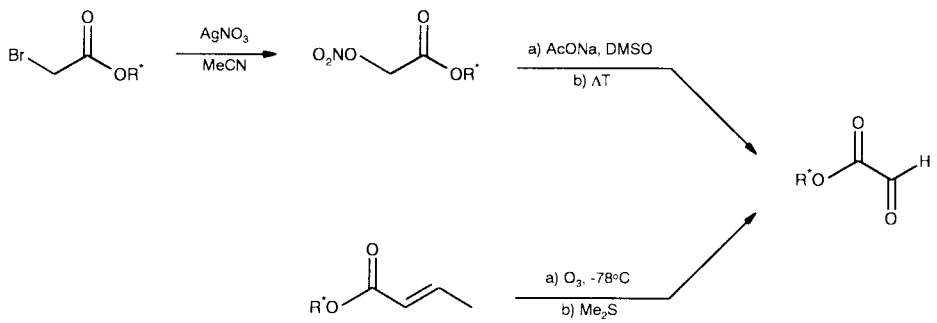
Abstract: Synthesis of chiral derivatives of glyoxylic acid with special emphasis on *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam is presented. Investigation of glyoxylic acid chiral derivatives in various stereocontrolled organic syntheses showed their excellent ability to provide products of high optical purity. Application of our methodology to the synthesis of natural products and their analogs is presented.

INTRODUCTION

Derivatives of glyoxylic acid and its simple analogs, such as pyruvic or phenylglyoxylic acid, readily available via reactions with chiral alcohols or amines, play an important role in stereocontrolled syntheses of various organic compounds. We turned our special attention on chiral esters and amides possessing reactive functionalities in the α-position as oxo and imino groups. These compounds allow for easy introduction of heterofunctionalities, often met in natural products and their analogs.

SYNTHESIS OF CHIRAL GLYOXYLATES

Chiral glyoxylates were synthesized from bromoacetates according to a classical Kornblum procedure [1] based on elimination of nitrite ion or, preferably, by ozonolysis of the double bond in respective chiral ester or amide of crotonic acid. The second method proved to be the most efficient one in the case of Oppolzer sultam's (**1**) derivatives [2].



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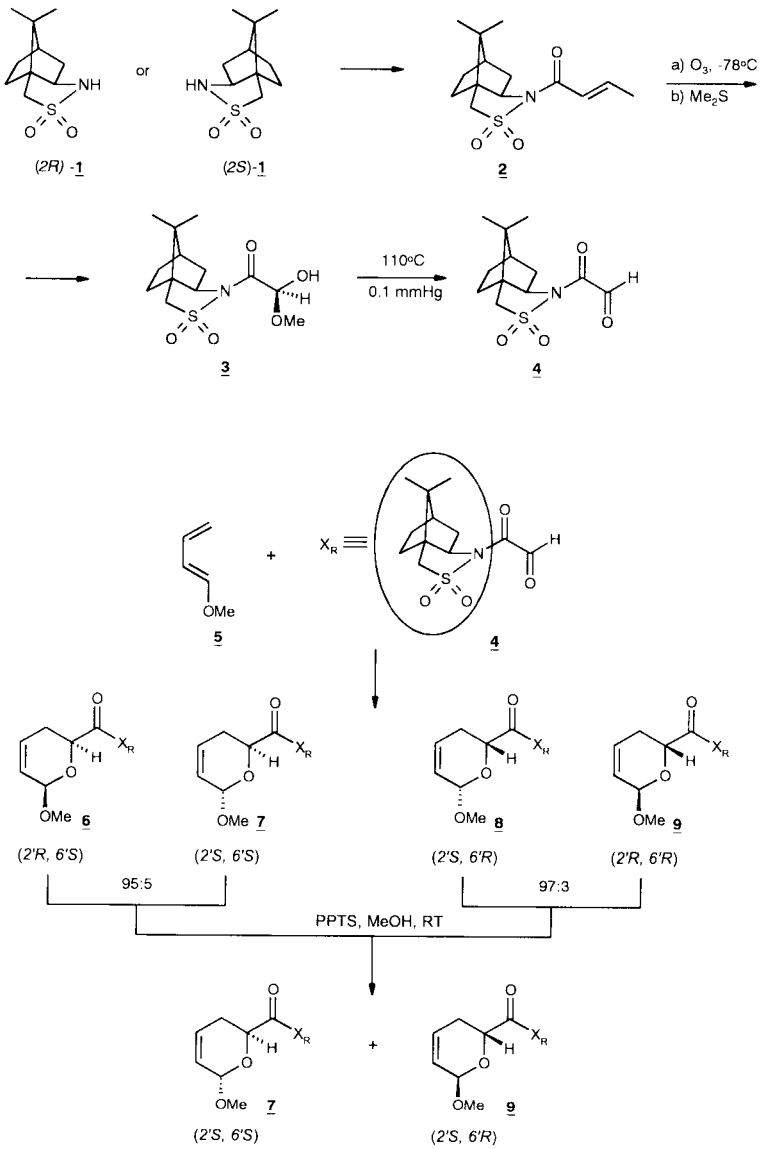
SYNTHESIS OF *N*-GLYOXYLOYL-(2*R*)-BORNANE-10,2-SULTAM

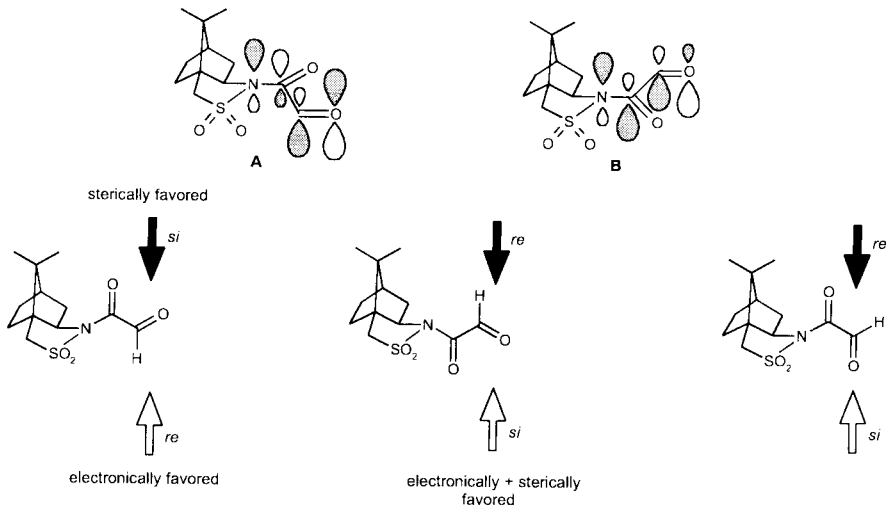
Several approaches to the synthesis of compound **4** were investigated and, finally, we found that the best method is the ozonolysis of crotonic acid derivative **2** performed in the mixture of methanol-methylene chloride. Usual work-up with dimethyl sulfide afforded stable, crystalline hemiacetal **3**, from which free aldehyde is liberated by heating at high vacuum [3]. It is worth saying that, due to equilibrium between **3** and **4**, in some reactions hemiacetal **3** can be used without need for thermal decomposition.



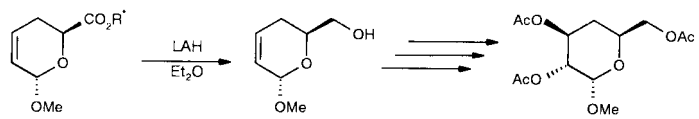
[4+2] CYCLOADDITION OF *N*-GLYOXYLOYL-(2*R*)-BORNANE-10,2-SULTAM

N-Glyoxyloyl-(2*R*)-bornane-10,2-sultam (**4**) was used in noncatalyzed atmospheric and high-pressure [4+2] cycloadditions to 1-methoxybutadiene-1,3 (**5**), yielding mixture of diastereoisomers **6**–**9** in good

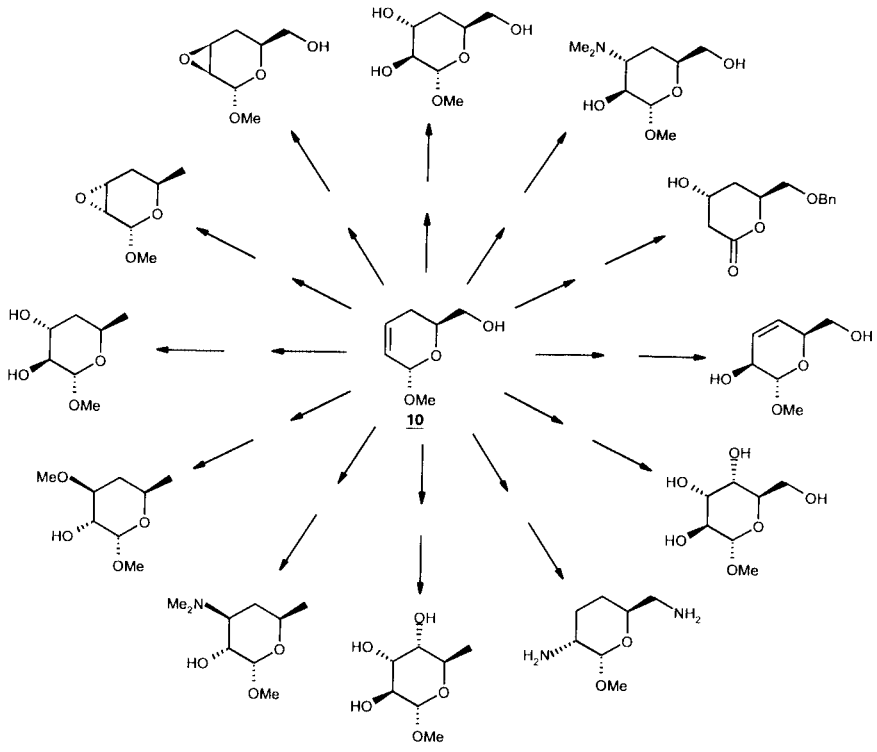
yield but low diastereoselectivity. The best results were obtained with 2% of $Eu(fod)_3$ as a weak Lewis acid catalyst (de 88%, 81% yield) [4]. The mixture of four crystalline diasteroisomeric adducts can be easily isomerized to *trans* adducts **7** and **9** with PPTS in methanol [5]. The major adduct is readily separated by recrystallization or column chromatography. Rationalization of the stereochemical outcome of the reaction is based on the steric and stereoelectronic effects, as presented below. The thermodynamically more stable conformer **A** is favored from the steric reasons, but recent calculations show that conformer **B** is the most reactive one, taking into account the level of the LUMO orbital and atomic coefficients. The stereoelectronic effect cooperates with steric effect in conformer **B**, thus enhancing its influence on the asymmetric induction [6].



The absolute configuration at C6 was established by X-ray analysis of both (2*S*,6*S*)- and (2*R*,6*R*)-diastereoisomers. Independently, the major cycloadduct was converted to the alcohol **10**, which, in turn, was already correlated to the known carbohydrate **11** [7].

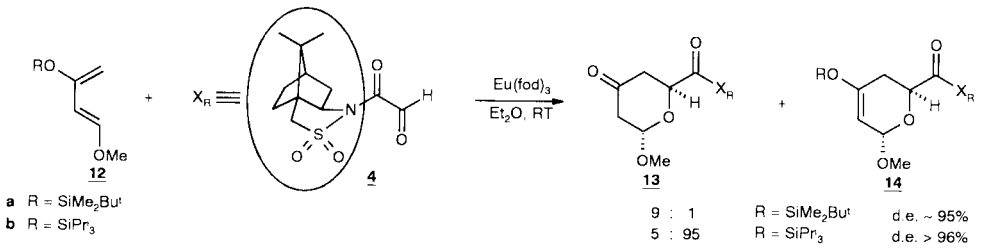


The enantiomerically pure alcohol **10** is a valuable starting material for the synthesis of natural products. Presence of the double bond in the dihydropyran ring and the hydroxyl group in the side chain of the ring allows for the introduction of hydroxy and amino functionalities, providing easy access to various natural and nonnatural monosaccharides. These possibilities were illustrated by the synthesis of optically pure compactin lactone [4b] and purpurosamine C [8]. The broad spectrum of synthetic targets, some of them already synthesized in our laboratory [9], is shown in the figure below.



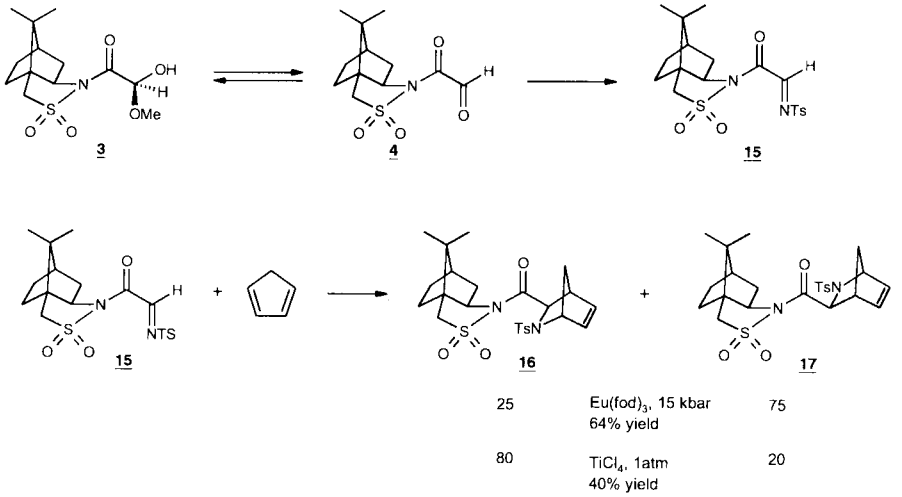
CYCLOCONDENSATION REACTION

The asymmetric cyclocondensation reactions of **4** with silylated dienes **12a** and **12b** were studied. For diene **12a** the desilylated product predominated. In the case of more stable diene **12b**, the primary cycloadduct was the major product. In each case, diastereoisomeric excess was over 95:5 [10].



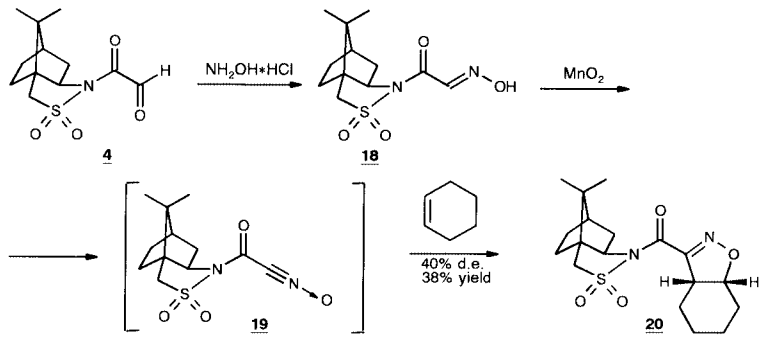
CYCLOADDITION OF GLYOXYLIC IMINES

The hetero-Diels–Alder reaction of imines with 1,3-dienes is a potential tool in the synthesis of six-membered heterocycles, being the backbone of several alkaloids and antiviral compounds. The imine **15**, derived from *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**4**) was subjected to the Lewis acid-catalyzed Diels–Alder reaction with cyclopentadiene, yielding cycloadducts **16** and **17** in a ratio 1:3 or 4:1, depending on the catalyst used. The direction of the asymmetric induction can be thus controlled by the choice of the Lewis acid [11].

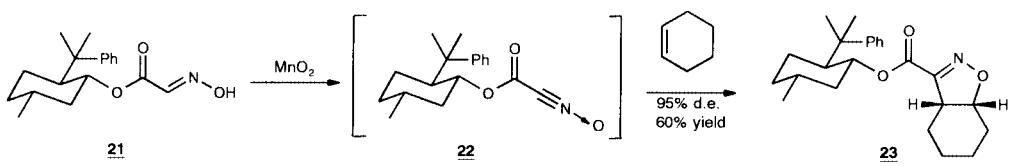


1,3-DIPOLAR CYCLOADDITION

1,3-Dipolar cycloaddition is an excellent method for the synthesis of heterocyclic compounds. We have investigated this reaction using nitrile oxides as dipoles. Nitrile oxides were synthesized by the MnO_2 oxidation of aldoximes obtained from glyoxylates. In the case of sultam-derived nitrile oxide **19** both chemical yield and diastereoisomeric excess were low [12].

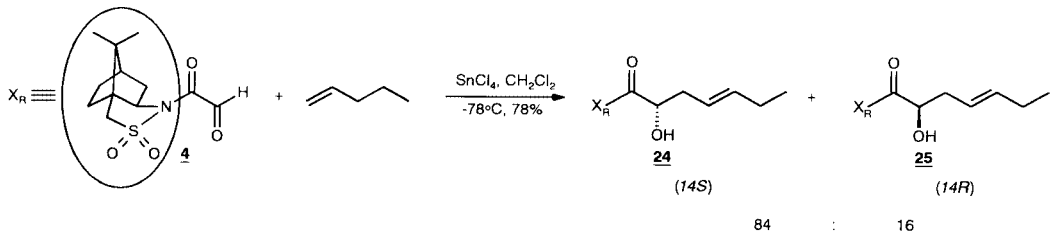


8-Phenylmenthyl glyoxylate-derived nitrile oxide **22** reacted with cyclohexene with good yield and very good diastereoselectivity [12b].



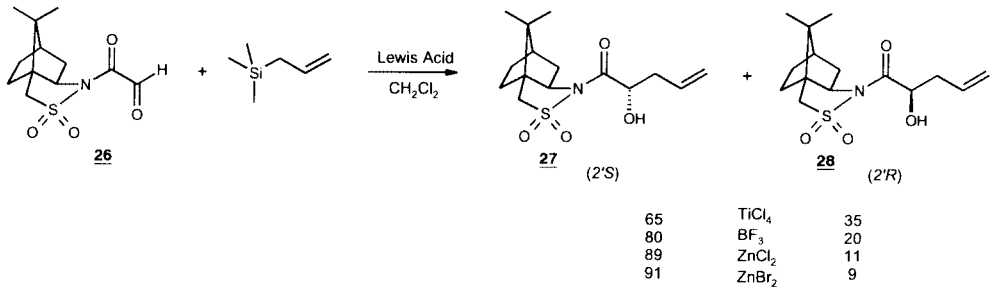
ENE REACTION

We have studied the ene reaction of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**4**) or its hemiacetal **5** with 1-pentene and 1-hexene. The yield and diastereoisomeric excess was highly dependent on the Lewis acid used. The best results were obtained when the reaction was catalyzed with 1.1 equiv. of $SnCl_4$, the reaction catalyzed by $ZnBr_2$ gave higher yields but with somewhat lower de. The absolute configuration of major diastereoisomer **24** was confirmed by X-ray analysis and chemical correlation [13].

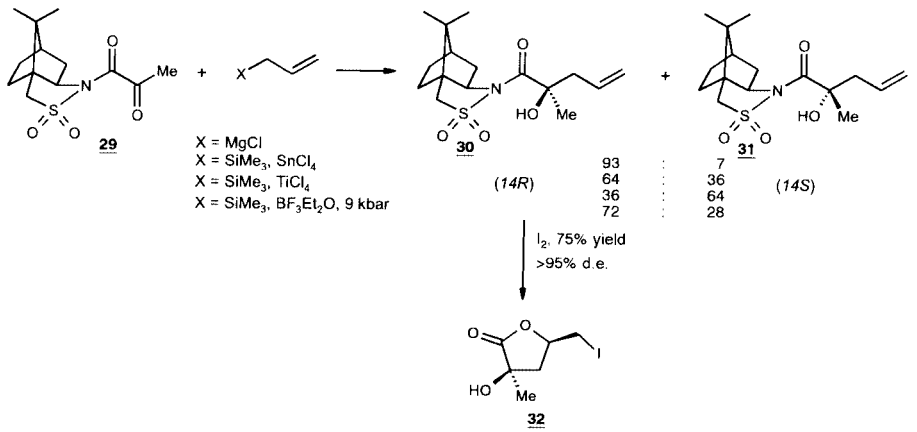


ALLYLIC ADDITIONS

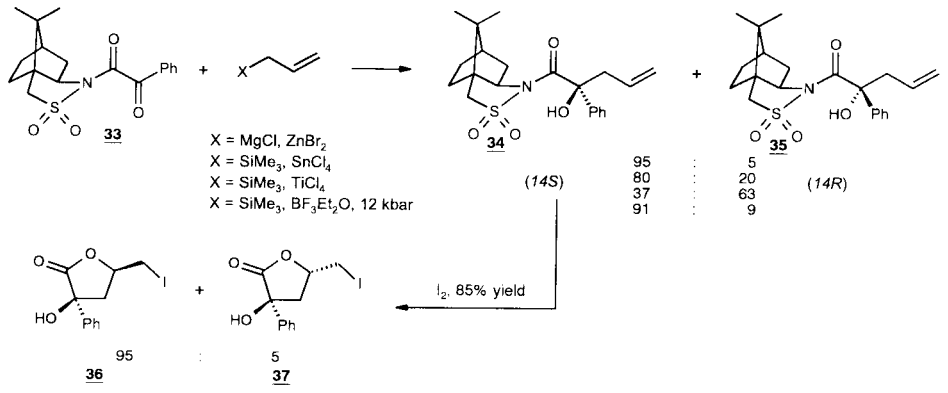
Additions of allylic reagents to derivatives of glyoxylic acid open an interesting synthetic route to various natural products. The best results in terms of both the chemical yield and diastereoisomeric excess were obtained when the addition was catalyzed by $ZnBr_2$ and when the hemiacetal **3** was used as a substrate. Major diastereoisomer **27** was converted to a useful chiral building block—(*S*)-1,2-pentanediol [14].



These good results prompted us to study addition of allylic reagents to α-ketoimides **29** and **33**. The addition creates quaternary chiral center in highly stereoselective manner. For the former one, the best diastereoisomeric excess was obtained for the noncatalyzed addition of Grignard reagent.

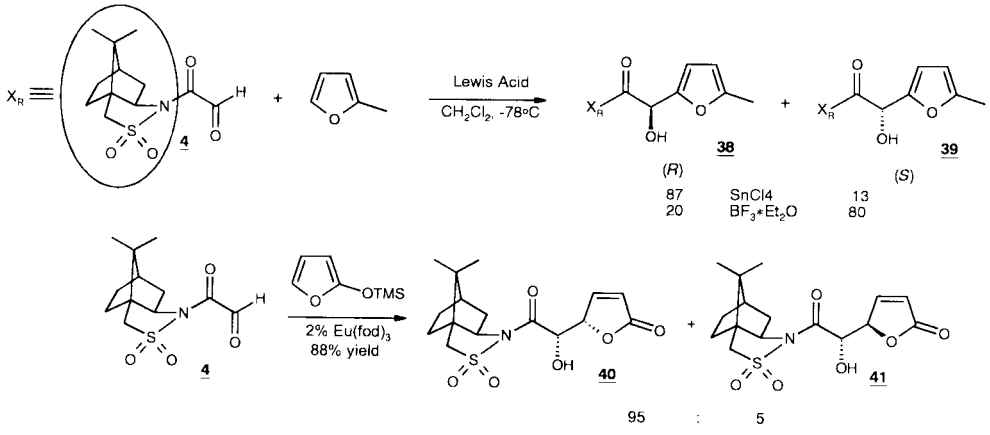


For the latter compound, addition of Lewis acid highly improved diastereoselectivity, and the best result was obtained in the presence of $ZnBr_2$. Major diastereoisomers from both reactions were efficiently and with high diastereoselectivity transformed into respective iodolactones [15].



FURAN CHEMISTRY

Addition of chiral aldehydes to furan or its 2-substituted derivatives provides chiral 2- or 2,5- substituted furans, respectively, which can be further elaborated to, for example, uloses. Lewis acid-catalyzed reaction of **4** with 2-methylfuran leads to two diastereoisomeric 2,5-substituted furans **38** and **39**. The configuration of the newly created stereogenic center can be controlled by the choice of the Lewis acid catalyst [16]. $Eu(fod)_3$ catalyzed addition to 2-trimethylsilyloxyfuran yields 4-substituted butenolides **40** and **41** with both high chemical yield and diastereoisomeric excess [17].



CONCLUSION

Chiral ester and amide derivatives of glyoxylic and pyruvic acids, as well as their simple analogs, constitute effective chirons, useful in the synthesis of chiral building blocks, auxiliaries, ligands, etc. For such preparations, many various organic reactions can be used due to high reactivity of these chirons and owing to their high diastereoselectivity.

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