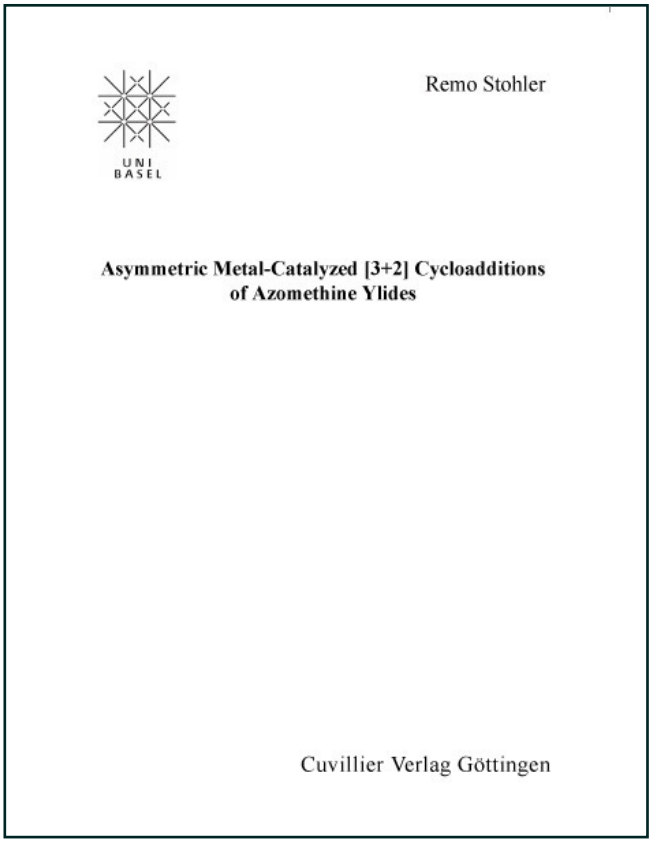
Asymmetric Metal-Catalyzed [3+2] Cycloadditions of Azomethine Ylides



1 Introduction

1.1 Racemic Versus Enantiopure Drugs

For a long time the decision whether a drug should be developed as a racemate or as an enantiopure compound was left to the institution producing the drug. The situation changed when it was realized that there is often a significant difference between the enantiomers of chiral drugs regarding their pharmacodynamic and pharmacokinetic properties. In addition recent advances in stereoselective synthesis and analysis of chiral molecules helped to make the decision in favour of enantioselective synthesis of chemical entities. At present no regulatory institution has an absolute requirement for the development of enantiopure drugs but if a racemate is presented for marketing then its use must be justified. Arguments like the individual isomers are stereochemically unstable and readily racemize *in vitro* and/or *in vivo* or the use of a racemate produces a superior therapeutic effect than either individual enantiomer could for instance support the submission of a racemates. However, the trend towards the development of enantiopure drugs is clearly visible and therefore further development of stereoselective synthesis is highly desirable. This will be demonstrated by the following examples.

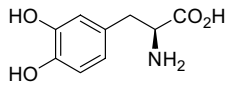
1.2 Different Pharmacokinetic Properties of Enantiomers

Since drug absorbtion, distribution, metabolism and excretion involve an interaction between the enantiomers of a drug and a chiral biological macromolecule it is hardly surprising that enantioselectivity is observed during these processes.

Absorbtion

The most important mechanism of drug absorbtion is passive diffusion through biological membranes. During this process there is generally little enantiomeric differentiation because it is dominated by the lipid and aqueous solubilities which are the same for both enantiomers.
One way of drug absorbtion which discriminates between enantiomers is the active transport process. L-dopa for instance (Figure 1), which is used in the treatment of Parkinson's disease, is rapidly absorbed from the gut by an active transport process, whereas D-dopa is slowly but

also completely absorbed by passive diffusion.[1] Large rate differences between passive and active transportation may result in a considerable difference of bioavailability.[2]

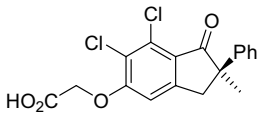


L-dopa

Figure 1.

Distribution

The majority of drugs undergo reversible binding to plasma proteins. Stereoselectivity can be observed in plasma protein binding to human serum albumin (HSA) and α_1-acid glycoprotein (AGP), the two most important plasma proteins with respect to drug binding. In general acidic drugs bind predominantly to HSA, whereas basic drugs bind predominantly to AGP, which is only present to the extent of 3% of HSA. The differences between the enantiomers in plasma protein binding are usually quite small. But also the low stereoselectivity in binding may have a significant effect on the amount of unbound drug in the plasma which is available for activity. In the case of indacrinone (Figure 2), which is used in the treatment of hypertension and congestive heart failure, the free fractions are 0.9% and 0.3% for the (*R*)- and (*S*)-enantiomer respectively.[3]



(*R*)-indacrinone

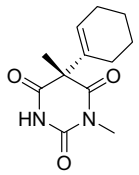
Figure 2.

Metabolism

Drug metabolism frequently shows stereoselectivity and involves the interaction with enzyme systems. Some enzymes are highly specialized whereas others like cytochrome P450 are multifunctional and accept a wide range of substrates. They usually show great substituent and stereochemical sensitivity including those systems that accept a wide range of substrates.

Examination of the stereochemistry of drug metabolism is of importance because individual enantiomers of a racemic drug may be metabolised by different routes to yield different products and they are frequently metabolised at different rates.

The (*S*)-enantiomer of barbiturate hexobarbital (Figure 3) has an elimination half-life which is three times longer than that of the (*R*)-enantiomer as a result of metabolic clearance.[4]



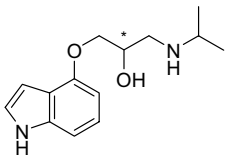
(*S*)-hexobarbital

Figure 3.

Excretion

Glomerular filtration, active secretion and passive and active reabsorbtion are the four major processes of renal excretion. In contrast to the active excretion processes no differences between the enantiomers are expected for the passive processes like glomerular filtration and passive reabsorbtion.

Since renal clearance of L-pindolol is faster than that of D-pindolol active renal secretion or renal metabolism is thought to be responsible for the differential clearance of the two enantiomers (Figure 4).[5]



Pindolol

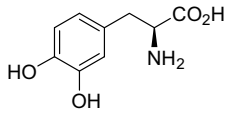
Figure 4.

1.3 Different Pharmacodynamic Properties of Enantiomers

The most important differentiation between enantiomers occurs at the level of receptor interactions. This leads to different pharmacodynamic properties of the enantiomers. Some of the possible situations are discussed below.

Only one enantiomer shows pharmacological activity

α-Methyldopa (Figure 5) is used against hypertension. The activity arises exclusively from the (*S*)-enantiomer[6] and it is therefore marketed as a single enantiomer.

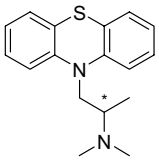


(*S*)-α-methyldopa

Figure 5.

Both enantiomers have similar activities

The enantiomers of the antihistamine promethazine (Figure 6) have similar pharmacological properties.[7]



promethazine

Figure 6.

The enantiomers have opposite effects

Dextropropoxyphene, exhibiting the (1*S*,2*R)*-configuration, is a useful painkiller whereas its enantiomer levopropoxyphene is an antitussive agent (Figure 7). Appropriately not only the molecules are mirror images but also their trade names DARVON®(dextropropoxyphene) and NOVRAD®(levopropoxyphene).[8]

dextropropoxyphene levopropoxyphene

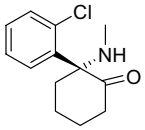
Figure 7.

One enantiomer antagonises the side effects of the other

Indacrinone (Figure 2) is an interesting example to show how the different modes of action of enantiomers can be used to create a more favourable profile of action of a drug by changing the ratio of the enantiomers. The (*R*)-enantiomer is a more potent natriuretic agent whereas the (*S*)-enantiomer is a more potent uricosuric agent. Following administration of the racemate to man the plasma half-life of the (*S*)-enantiomer is much shorter than that of the (*R*)-enantiomer (2-5 h, compared to the (*R*), 10-12 h). Hence its uricosuric activity is too short to prevent the undesirable rise in uric acid concentration. Alteration of the enantiomeric composition of the drug from the 1:1 ratio by increasing the proportion of the (*S*)-enantiomer resulted in a mixture (*S* : *R* : 4 : 1) which was isouricemic.[9] In other words one enantiomer is used to prevent the side effects caused by the other enantiomer.

Both enantiomers show activity but the adverse effects are predominantly associated with one enantiomer

Ketamine (Figure 8) is a general anaesthetic agent with painkilling properties. The drug exhibits stereoselective actions in both main-effect and the most important side-effects. The most unwanted side effects originate from the less potent enantiomer for the main-effects, the (*R*)-enantiomer.[10]



(*R*)-ketamine

Figure 8.

Chapter 2

Biological Activity of Pyrrolidines and Resulting Objectives

2 Biological Activity of Pyrrolidines and Resulting Objectives

2.1 Biological Active Pyrrolidines

Worldwide about 170 million individuals are afflicted with chronic hepatitis C[11], a viral disease that is caused by a hepatotropic virus called Hepatitis C virus (HCV). The infection can cause liver inflammation and might progress to cirrhosis or also liver cancer. The latter two are the major causes of morbidity and mortality.

The treatment of the disease with a combination of PEG-interferon-α and ribavirin is not always successful and shows severe side effects.[12] Therefore the identification of more effective treatments is essential.

Only recently it was reported that acyl pyrrolidines inhibit the Hepatits C NS5B polymerase whereas only one enantiomer showed a significant biological activity (Figure 9).[13]

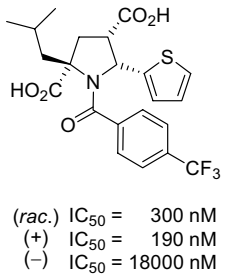
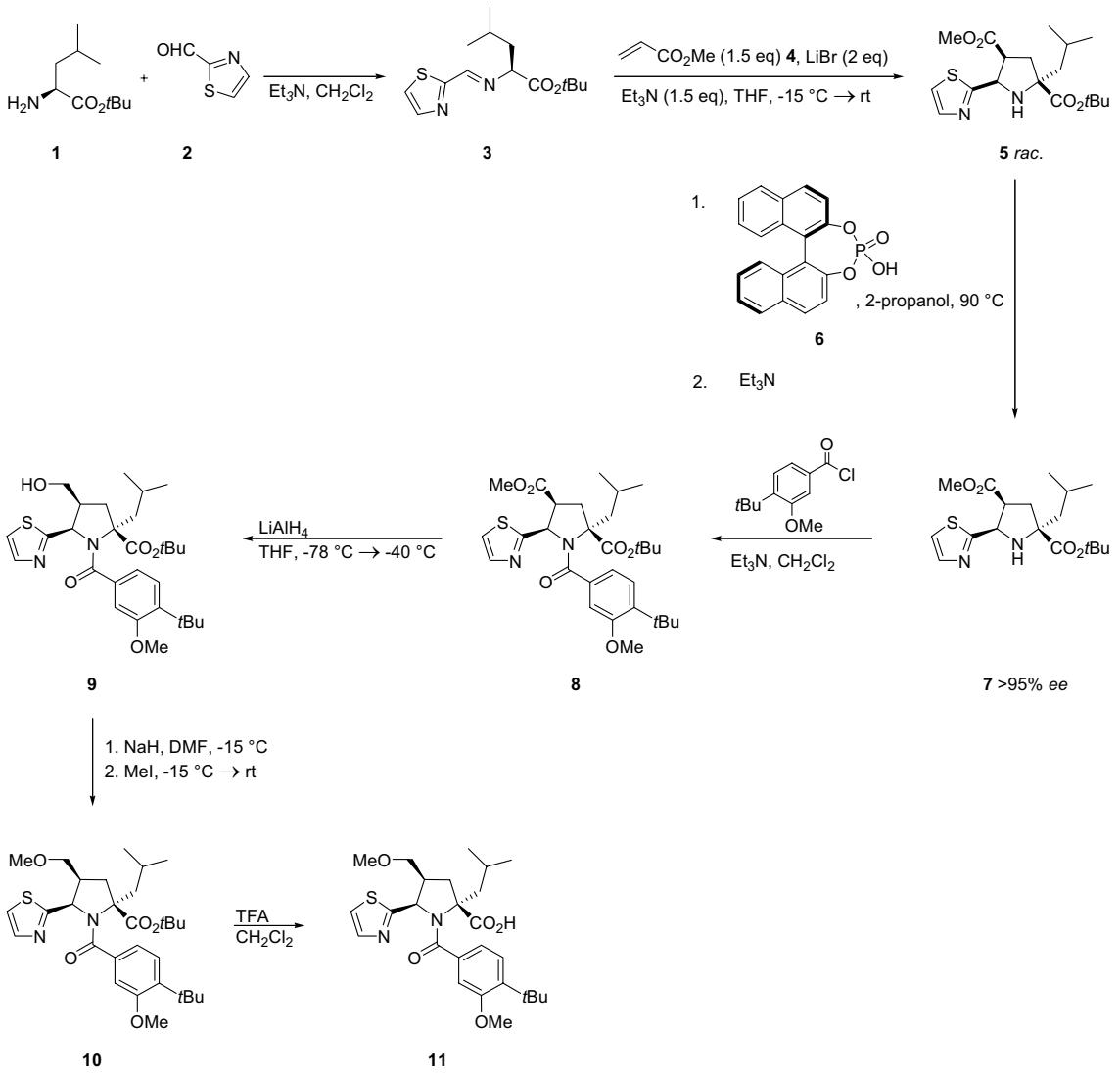


Figure 9.

Optimization of the substitution –pattern further increased the compounds' potency.[14] The synthesis of such an optimized pyrrolidine moiety **11** is illustrated in Scheme 1.[15] Subsequent to the formation of the imine **3** 2 equivalents of lithium bromide were used to promote the 1,3-dipolar cycloaddition reaction between the imine **3** and methyl acrylate **4** under basic conditions in THF. The racemic *endo* pyrrolidine species **5** was resolved into its enantiomers by diastereomeric salt formation using the chiral acid, *R*-BINAP phosphate **6.** The resulting salt was treated with triethylamine to obtain the chiral pyrrolidine **7** with a yield of 82% and an enantioselectivity of >95%. Further transformations led to the desired pyrrolidine moiety **11** with an overall yield of >25% in a 7 step sequence.



Scheme 1.

The [3+2] cycloaddition of the Scheme above might alternatively be performed by an asymmetric metal-catalyzed 1,3-dipolar cycloaddition reaction. This could then lead directly to the enantioenriched compound without the time consuming resolution step by diastereomeric salt formation.

Chiral pyrrolidines are present in many other biologically active compounds.[16] Therefore, the development of enantioselective catalysts for [3+2] cycloaddition leading to this ring system is highly desirable.