Stereoselective Syntheses of 2-Imidazolines

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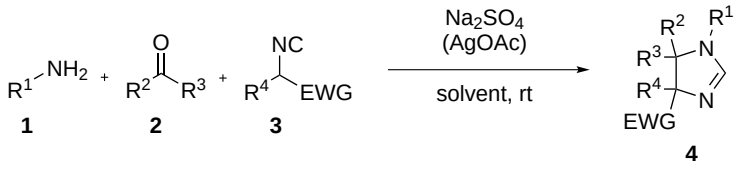
Summary

2-Imidazolines are a class of *N*-heterocycles that is studied for their broad range of biological activities and application as ligands or organocatalysts in asymmetric catalysis. Although already a number of enantioselective syntheses are known for 2-imidazolines, they often suffer from limitations in scope. This thesis describes several approaches aiming for new enantioselective syntheses of 2-imidazolines. The investigated strategies are all based on the imidazoline-3CR that was developed earlier in our group.

Chapter 1 first describes the relevance of the 2-imidazolines scaffold in medicinal chemistry and catalysis, complemented with an overview of the current methods for the enantioselective synthesis of 2-imidazolines.

Imidazoline-3CR

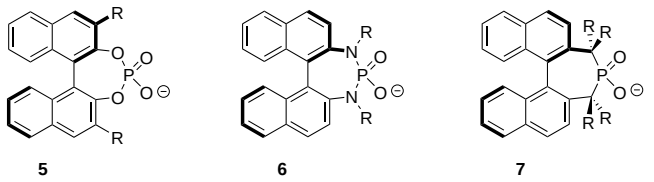
The imidazoline-3CR is a versatile (silver(I) catalyzed) multicomponent reaction (MCR) for the synthesis of 2-imidazolines **4** from amines **1**, ketones or aldehydes **2** and α-acidic isocyanides **3** (Scheme 1). The reaction displays a broad scope in all reactants, making this reaction valuable for the synthesis of structurally diverse imidazolines. An asymmetric variant of this reaction increases its applicability as it allows for easy access of structurally divers optically pure 2-imidazolines.



Scheme 1: The previously developed imidazoline-3CR.

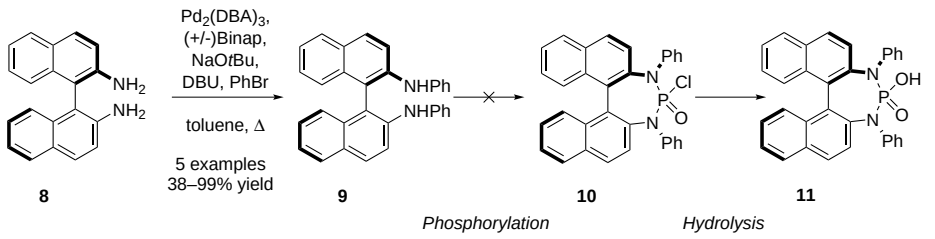
Asymmetric Catalysis

The research described in chapter 2 deals with a study toward an asymmetric imidazoline-3CR using catalysis. For this purpose, we employed the relatively new concept of asymmetric counteranion–directed catalysis. In this approach, a chiral environment is created by ion-pairing of a cationic intermediate with chiral anion in the enantiodetermining step. In this type catalysis, chiral *C*2-symmetric binol-based phosphates **5** are frequently used as chiral anions (Scheme 2). These phosphates **5** require large R-groups on the 3/3′-position of the naphthyl backbone, in order to create a chiral environment around the phosphate.



Scheme 2: Binol-based phosphates **5** and analogous structures.

We first aimed to synthesize analogues anions **6** and **7** as a new class of chiral anions. Placement of the directing groups to the atoms adjacent of the phosphorous result in a more pronounced chiral environment that should allow for a better enantiocontrol.

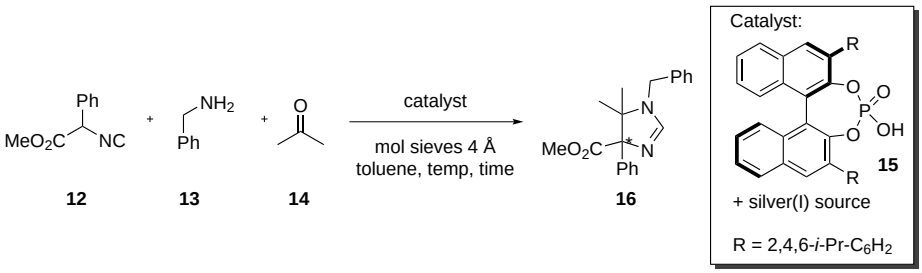


Scheme 3: Synthesis of the chiral phosphordiamidic acid **11**.

The synthesis was started from optically pure diamine **8**. A Buchwald-Hartwig coupling was used to introduce various dir-

ecting groups in reasonable to good yield (**9**, 38–99%, Scheme 3). However, in the next step phosphorylation of **9** to give **10** was troublesome, and all attempts using several phosphorylation agents failed. Therefore, the development of this route for the synthesis of **6**, as well as the carbon analogue **7** was abandoned.

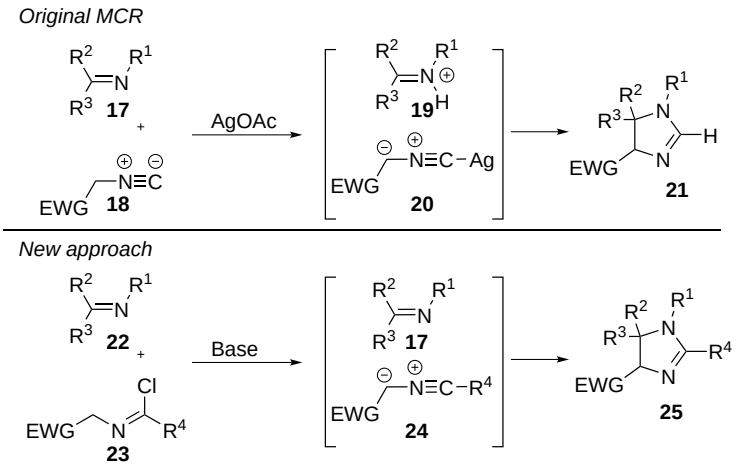
For the investigations to develop an asymmetric catalytic imidazoline-3CR, we selected the reaction in Scheme 4 as the benchmark reaction, using phosphoric acid **15** and a silver(I) source as the catalyst. After an optimization study of the reaction conditions, the best obtained *ee* for the formation of **16** was 27%. The *ee*, however, appeared to be dependent on the R-groups of the reactants as became clear when studying the scope of the reaction. Although R-groups were allowed and enantioselectivity was observed, the *ee* of the products was in neither of the reaction higher than 27%.



Scheme 4: Benchmark reaction for the development of the asymmetric catalysis.

Diastereoselective 1,3-Dipolar Cycloaddition

Our investigations for the synthesis of tetrafunctionalized 2-imidazolines in one step, is described in Chapter 3. We reasoned that the structurally similar nitrile ylids **25** could undergo the same type of 1,3-dipolar cycloaddition to imines **17** as silver-activated isocyanides **20** do in the imidazoline-3CR (Scheme 5).

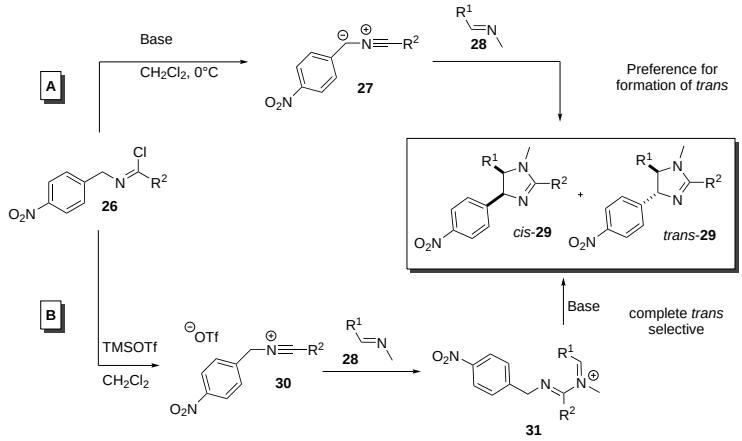


Scheme 5: Approach for the one-step synthesis of tetrafunctionalized 2-imidazolines.

Using *in situ* generated nitrile ylids **28** in the presence of imines **29** afforded imidazolines **30** in moderate yields (19–60%) in an optimization study (Scheme 6A). The products are formed wit the preference for the *trans*-isomer (d.r. = 33:67–<5:95). The scope was rather limited as the *p*-nitrophenyl group on the imidoyl chloride is essential for the reaction. For R^2, Ph or *p*-nitrophenyl was allowed, while on the imine (R^1) only electron poor aromatic groups are allowed.

Computations show that a step-wise reaction mechanism is likely to occur, in which the energy difference for the cyclization step toward the *cis*- and *trans*2-imidazolines **29** accounts for the diastereoselectivity.

In order to improve the yield and diastereoselectivity, an alternative "forced" stepwise reaction pathway was also investigated (Scheme 6B). The use of nitrilium ions **30** rather than nitrile ylids **27** in the reaction with imines **28** result in *N*-imidoyl iminium ion **31**, that upon deprotonation, readily cyclyzes to imidazolines **29**. This strategy indeed proved successful as the products were obtained as single diastereomers (d.r. = >5:95) in moderate to good yields (35–85%). Although this reaction still required the *p*-



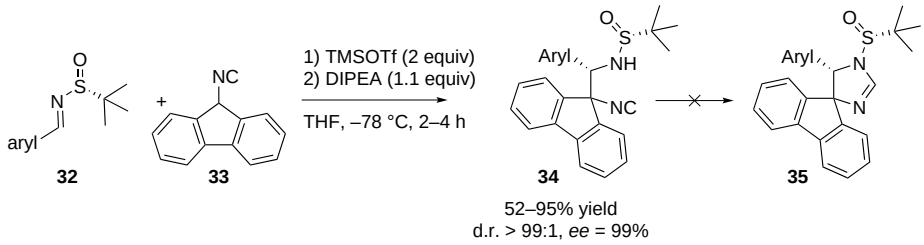
Scheme 6: Alternative approach for the one-step synthesis of tetrafunctionalized 2-imidazolines.

nitrophenyl group on the imidoylchloride, the scope for variation of R^1 and R^2 was slightly better.

Chiral Auxiliary

Another attractive approach in enantioselective synthesis is the use of chiral auxiliaries and is presented in Chapter 4. For application in the imidazoline-3CR we envisoned chiral sulfinyl group on sulfinimine **32** as suitable auxiliary, that can be easily recovered after removal from the product. An optimization study of the reaction conditions was performed. With the optimal conditions, various pre-formed aromatic sulfinimines **32** reacted smoothly with 9-isocyanofluorene (**33**), to afford β-sulfinylaminoisocyanides **34** in reasonable to good yield and with full diastereoselectivity (Scheme 7). The reason that isocyanides **34** are obtained instead of the imidazolines **35** can be explained by the relatively low nucleophilic character of the sulfinamide nitrogen atom toward cyclization.

Deptrotection of **34** using HCl in Et_2O, followed by treatment with Et_3N allowed the efficient formation of optically pure *N*-unsubstituted 2-imidazolines **35** in quantitative yield (Scheme 8).



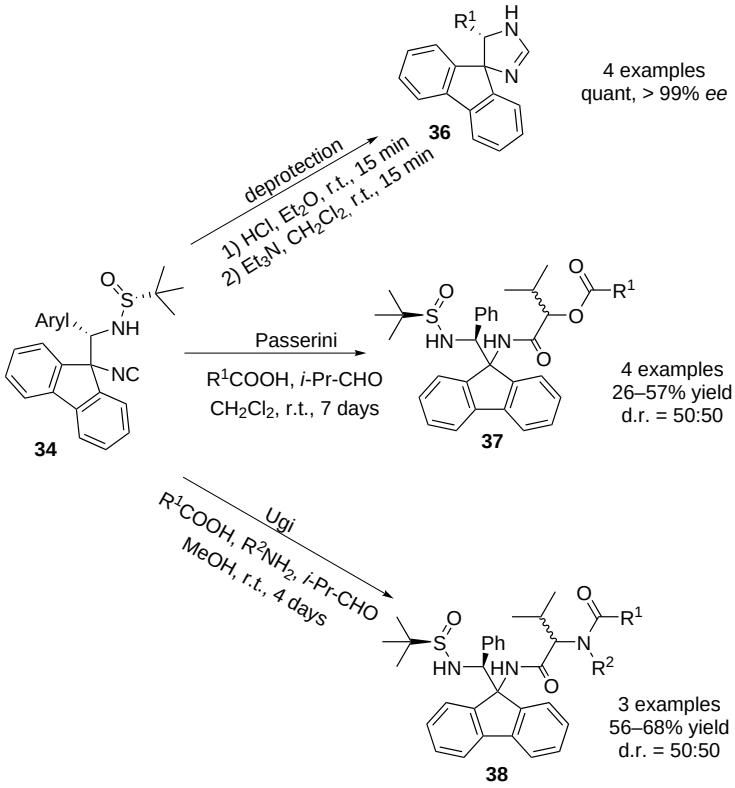
Scheme 7: Synthesis of β-sulfinylamino isocyanides **34**.

We also investigated the use of the optically pure **34** in the isocyanide based Passerini and Ugi MCRs. Although slowly under the typical reaction conditions for these reactions, the MCR products **36** and **37** were obtained in reasonable yields. Unfortunately, the chirality of the isocyanide did not influence the formation of the newly formed stereocenters as all the MCR products were obtained as a 1:1 mixture of diastereomers.

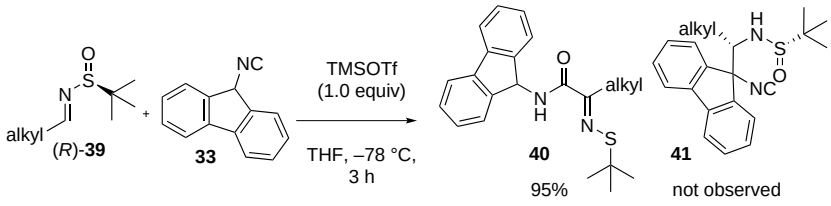
Chemoselective formation of α-Sulfeneimino Acetamides

In Chapter 5, the remarkable chemoselective formation of α-sulfenimino acetamides **40** instead of β-sulfinylamino isocyanides **41** is described (Scheme 9). When aliphatic sulfinimines **39** were reacted with 9-isocyanofluorene **33** a complete switch in the reaction pathway was observed.

A mechanism is suggested for this transformation that is supported by computations. The reaction proceeds *via* initial attack of the terminal isocyanide carbon atom on the sulfinimine instead of attack of the deprotonated α-carbon atom, followed by a cascade of steps resulting in **40**. An additional computational study was performed to explain observed selectivity. For the attack of a terminal isocyanide carbon atom to aromatic sulfinimines **32**, a much higher barrier was found compared to that of aliphatic sulfinimines **39**. Finally a scope study was performed and showed that both variation of the imine and the isocyanide is extensively possible.



Scheme 8: Isocyanide-based follow-up chemistry with β-sulfinylamino isocyanides **34**.



Scheme 9: Chemoselective formation of α-sulfenimino acetamides **40**.