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The asymmetric reduction of imidazolinones with trichlorosilane†

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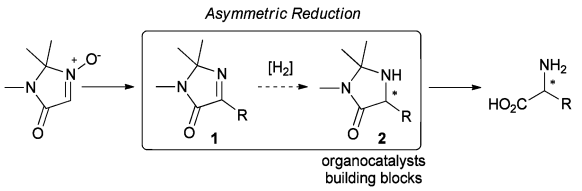
It is shown how imidazolinones are reduced by trichlorosilane in a highly enantioselective fashion when treated with a novel Lewis base organocatalyst that is based on a 2,2′-bispyrrolidine core. Under mild reaction conditions and with low catalyst loading the hydrosilylation reaction provides a broad range of chiral imidazolidinones with various structural motifs including sterically demanding substituents, alkyls and aryls.



Scheme 1 The reduction of imidazolinones.

Chiral α-amino acids are fundamentally important structural motifs.[1] A great range of synthesis methods have been developed over the last decades with the goal not only to grant *de novo* access to naturally occurring α-amino acids and their enantiomers, but particularly to provide access to unnatural amino acid derivatives.[2] Important catalytic strategies for the asymmetric synthesis of α-amino acids are, amongst others,[2b,3] the hydrogenation of dehydroamino acids,[4] the Strecker reaction[5] and the electrophilic alkylation of glycine derivatives with chiral phase-transfer catalysts.[6]

We became interested in the *de novo* synthesis of functionalized α-amino acids when studying small peptide catalysts with artificial amino acids for their use in site-selective reactions.[7] At the beginning of our studies in the field, we felt that the enantioselective reduction of the imidazolinone core **1** would provide a straightforward entry into chiral α-amino acids: the imidazolinone substrates **1** can be easily generated with all variants regarding the substituent R,[8] and the imidazolidinone products **2** can be certainly hydrolyzed to the desired α-amino acids (Scheme 1).[9] Moreover, the chiral imidazolidinones are widely appreciated heterocycles due to their value as chiral organocatalysts[10] and their use as building blocks for the synthesis of pharmaceuticals.[11]

To our surprise, the reduction of imidazolinones was hardly attempted,[12] and our literature search on stereocontrolled variants was of no avail. We then began our studies on the catalytic asymmetric reduction of imidazolinones by employing several catalyzed hydrogenation conditions, *i.e.* transition metal-catalyzed with Ru-[13] and Rh-complexes[14] and Brønsted acid-catalyzed transfer hydrogenation.[15] While all of those early attempts led to unusable conversions or shockingly low enantioselectivities, the results with trichlorosilane and Lewis base catalysts were, at least, promising.

Trichlorosilane ($HSiCl_3$) is a remarkable, and still somewhat underused reducing agent: it is a truly cheap reagent prepared in the silicon industry that requires activation through coordination with a Lewis base to generate the actual reducing species.[16] Despite the fact that the trichlorosilane reduction methods produce some quantities of halogen waste, the Lewis base-catalyzed conditions benefit from being metal-free and mild. Trichlorosilane has been extensively used for the reduction of C=N bonds[17] and, to some lower extend, for the reduction of C=O bonds[18] and heterocycles.[19] In combination with chiral Lewis base organocatalysts, a number of asymmetric reductions were reported; the catalyst design is typically comprised of either *N*-formyl amino acid derived carboxamides or picolinamides,[16c] and chiral sulfonamides have attracted recent interest too.[20]

We now show that trichlorosilane is ideally suited for the challenging reduction of imidazolinones. We also present a new organocatalyst that allows for the asymmetric reduction of the imidazolinone core at low catalyst loading: a broad range of chiral imidazolidinones can be easily formed with excellent enantioselectivities.

Our studies on the trichlorosilane reduction of imidazolinones began with a preliminary screening for enantioselectivity: several

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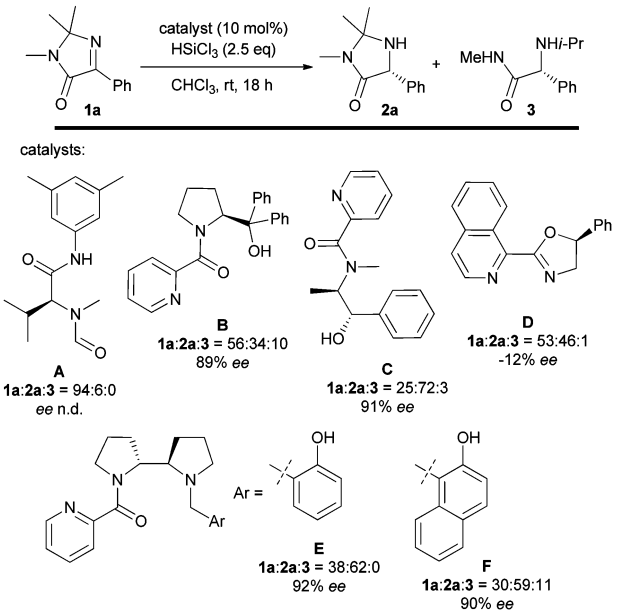
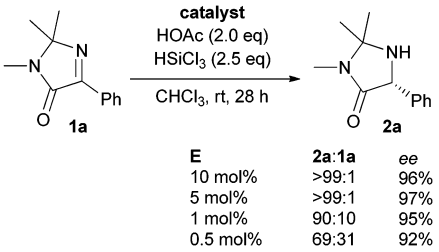


Scheme 2 Initial screening for enantioselectivity.

organocatalysts, most of which were previously reported in the literature for reductions with trichlorosilane, were tested in the reaction of phenyl-substituted imidazolinone **1a** in $CHCl_3$ at room temperature. An excerpt of those results is shown in Scheme 2 demonstrating that the widely used *N*-formyl derivative **A**[21] and oxazoline derivative **D**[22] results in poor enantioselectivity while the known picolinamides **B**[23] and **C**[24] lead to imidazolidinone **2a** formation with good enantioselectivities. We also found that the new picolinamide **E** (and its congener **F**) based on a chiral bispyrrolidine core gave the desired product with similar enantioselectivity after 18 h.[25,26] A typical side product of the reaction was the acyclic amino acid derivative **3**.

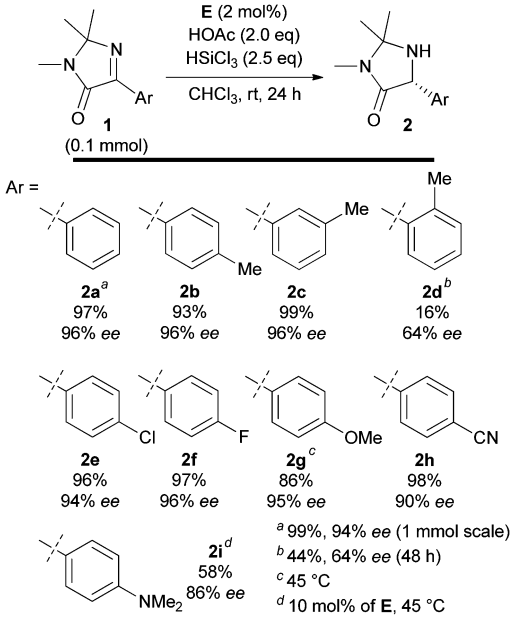
We then decided to optimize the reaction with newly developed catalyst **E**. It was found that only chlorinated solvents (*i.e.*, CH_2Cl_2, $CHCl_3$) were suited with $CHCl_3$ being slightly superior in terms of yield; other solvents led to unsatisfactory enantioselectivities (*e.g.* toluene, THF, MeCN, *n*-heptane, MeOH). The reaction temperature influenced the enantioselectivity only in a minor way; the conversion at below 0 °C, however, was at an impractically low rate. For convenience, we therefore decided to run the reductions at room temperature. In the course of our optimization study, we found that the addition of acid additives was of utmost importance with respect to the reproducibility of the reaction, in particular regarding to the ratio **2a**/**3**: we used a standard procedure where 2.0 equivalents of acetic acid are added to the reaction mixture. Under these conditions, the formation of side product **3** was never observed. However, the addition of acid additives led to a decrease of enantioselectivity with catalyst **C** (89% ee) while the new catalysts **E** exhibited an even higher efficacy (96% ee). We also note that pretty low catalyst loadings were feasible without shrinkage of the enantioselection. At 10 mol% and 5 mol%, the smooth reaction resulted in almost quantitative product formation in >95% ee while at a lower catalyst loading, a decrease in conversion was naturally



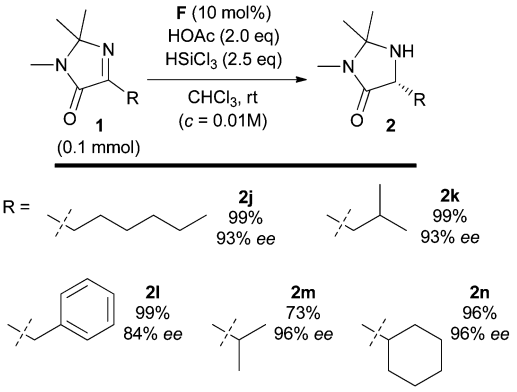
Scheme 3 Influence of the catalyst loading.

observed (Scheme 3). Nevertheless, a high enantiopurity was observed even with 1 mol% of catalyst **E**, and the formation of undesired by-products was hardly detected under any conditions (by ^1H NMR).

With useful conditions in hand, we explored the scope of the Lewis base-catalyzed hydrosylilation of imidazolinones. On a 0.1 mmol scale, a range of heterocyclic substrates **1** bearing aromatic substituents (R = aryl) were treated with trichlorosilane (2.5 equiv.) and acetic acid (2.0 equiv.) in chloroform (0.1 M) at room temperature. In general, 2 mol% of catalyst **E** were employed, and the reactions were run for 24 h to ensure complete conversion of the starting substrates. As summarized in Scheme 4, *para*- and *meta*-methylated phenyl substrates **1b** and **1c** afforded the products in excellent yields with good enantioselectivities. However, *ortho* substitution of the phenyl group decreased the degree of enantioselection dramatically, and a lower conversion was observed after 24 h. Electron-donating and electron-withdrawing substituents were suitable, albeit with slightly lower enantioselection in the case of cyano-substituted substrate **1h**. A limitation was only found with dimethylamino-substituted substrate **1i** where product formation was slow even at 45 °C with 10 mol% of the catalyst, although an acceptable enantioselectivity (*i.e.*, 86% ee) was reached in this



Scheme 4 Scope with arylated substrates.



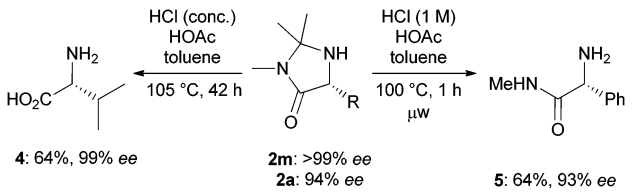
Scheme 5 Scope with alkylated substrates.

case, too. It was assumed that the Lewis base nature of the dimethylamino substituent was competitive with the catalyst with regard to the coordination of the trichlorosilane reagent.

We also demonstrated that the method is suitable for the preparation of larger scale quantities of chiral imidazolidinones. For example, 1.0 mmol of imidazolinone **1a** were smoothly transformed with 2.5 equiv. of $HSiCl_3$, 2.0 equiv. of HOAc, 0.02 equiv. of **E** at room temperature in $CHCl_3$, providing **2a** in 99% isolated yield and with 94% ee (Scheme 4).

When attempting the asymmetric reduction of alkyl-substituted imidazolinones (R = alkyl), we realized that the uncatalyzed hydrosilylation became an important factor that led to lowered enantioselectivities. We then decided to react the alkyl-substituted substrates at a 10-fold lower concentration (*i.e.*, 0.01 M instead of 0.1 M), where the background reaction was found to be almost completely suppressed, a precaution that was not necessary with the aryl-substituted substrates that showed no conversion in the absence of Lewis base catalysts. We also found that catalyst **F** possessing a naphthol core had a slightly better performance than catalyst **E** with the phenol core under the reaction conditions. Its use (10 mol%) together with $HSiCl_3$ (2.5 equiv.) and HOAc (2.0 equiv.) in $CHCl_3$ (0.01 M) at room temperature gave access to several chiral imidazolidinones having alkyl groups (Scheme 5). For example, imidazolidinone **2j** with R = *n*-hexyl was obtained in 99% isolated yield and 93% ee. Substrates with sterically more demanding alkyl groups (*e.g.*, i-Pr, **1m**; Cy, **1n**) also afforded the desired products in good yields and with high ee values.

The chiral imidazolidinone heterocycles are appreciated as valuable in themselves. However, we also briefly studied the liberation of enantiomerically enriched amino acids from the chiral imidazolidinone heterocycles (Scheme 6). Under strongly acidic conditions at 105 °C for 42 h, the aliphatic amino acid



Scheme 6 Synthetic use of chiral imidazolidinones.

D-valine was obtained from **2m**[27] without detectable loss of the enantiomeric excess. As known from various reports,[3a,12] aryl-glycines are somewhat more difficult to access in enantiopure form since they are prone to racemization due to the high acidity of the α-aryl proton.[2b,28] Accordingly, the harsh acidic conditions used for the liberation of D-valine (**4**) led to an erosion of enantiopurity when applied to the generation of D-phenylglycine from **2a**: 78% ee were achieved in this case. However, we were able to generate the D-phenylglycine methyl amide in moderate yield through the cleavage of the *N*,*O*-acetal under milder conditions using diluted hydrochloric acid (1 M, aqueous) for only 1 h at 100 °C. Of importance, no loss of enantiopurity was observed for the conversion of **2a** into **5**.

In summary, we have shown the first asymmetric reduction of imidazolinones using trichlorosilane as the hydride source and a new Lewis base organocatalyst. The catalyst, easily derived from a chiral 2,2′-bispyrrolidine core, promoted the hydrosilylation of a broad range of substrates, and the imidazolidinone products were obtained in high yields and excellent ee-values under mild conditions. Further investigations devoted to the application scope of the catalyst are part of our current research.

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