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Mimicking enzymatic transaminations: attempts to understand and develop a catalytic asymmetric approach to chiral α-amino acids

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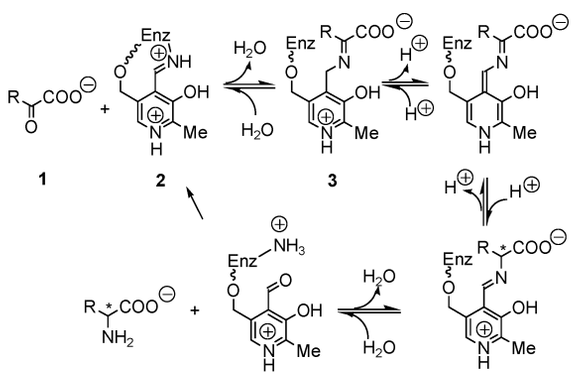
Attempts are made to build a bridge between asymmetric catalysis and enzymatic reactions by mechanistic investigations and the development of a catalytic and enantioselective approach to amination of α-keto esters by primary amines catalyzed by chiral Lewis acids as a model for transamination enzymes. Different Lewis acids can catalyze the half-transamination of α-keto esters using primary amine nitrogen sources such as pyridoxamine and 4-picolylamine. The mechanistic studies of the Lewis-acid catalyzed half-transamination using deuterium-labelled compounds show the incorporation of deuterium atoms in several positions of the α-amino acid derivative, indicating that the enol of the α-keto ester plays an important role along the reaction path. The catalytic enantioselective reactions are dependent on the pK_a-value of the solvent since enantioselectivities were only obtained in solvents with high pK_a-values relative to methanol. However, stronger acidic conditions generally gave better yields, but poor enantioselectivities. A series of chiral Lewis acids were screened as catalysts for the enantioselective half-transamination reactions and moderate yields and enantioselectivities of up to 46% ee were obtained.

Introduction

Mimicking biological systems in the laboratory by "simple organic molecules and catalytic systems" is difficult to achieve in general. First of all, the detailed reaction mechanisms in biological systems are often only partially elucidated and are complicated compared to the detailed insight chemists normally have into reaction mechanisms. Second, enzymatically driven reactions usually have a ΔG-value close to 0 kcal mol^{-1}, and therefore the reactions can proceed in both directions. Such reactions are thus difficult to catalyze in the desired direction, as the catalyst might also promote the reverse reaction. Third, reactions in biological systems take place in water, and water acting as solvent in combination with chiral metal catalysts is generally problematic. Either the catalyst and/or substrate are not soluble in water, or the catalyst is deactivated by water. Therefore, if one wants to perform catalytic enantioselective reactions in water, either specifically modified water-soluble catalysts, or different approaches in organic solvents are required.[1]

The biological transformation of α-keto acids **1** to α-amino acids **5** (also known as half-transamination[2a]) is catalyzed by vitamin B_6-dependent aminotransferase.[2] This transformation proceeds *via* ketimine **3** which is stereoselectively protonated to give the optically active α-amino acid fragment as aldimine **4**. The transamination of **1** to α-amino acids **5** takes place *via* several protonation/isomerisation steps as outlined in Scheme 1.

The transamination enzyme ensures formation of the optimal geometry for the protonation/isomerization steps and incorporates the base for deprotonation. However, optimal geometry is one of the most important factors for these reactions and for pyridoxal phosphate (PLP) dependent enzymes in general. The PLP-dependent enzymes labilize one of the three bonds of the α-carbon atom of an amino acid substrate (Fig. 1). The bond *a* is labilized by aminotransferase, bond *b* by decarboxylases and bond *c* by aldolases.[3] It has been stated that an important principle for bond breaking is that the bond being broken must be perpendicular to the π-orbitals of the PLP-pyridine ring.[3] In the aminotransferase (bond *a*) this



Scheme 1 Mechanism of the natural enzyme controlled half-transamination (Enz = enzyme).

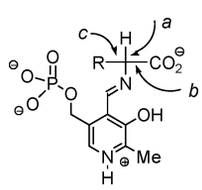


Fig. 1 Influence of PLP-dependent enzymes on the lability of the different bonds on the α-carbon atom of an amino acid substrate.

is accomplished by binding the amino acid substrate with the C_α–H bond perpendicular to the PLP-ring, *i.e.* the choice of one of the three possible catalytic outcomes is determined by stereoelectronic effects.[3]

The non-enzymatic transamination of α-keto acids with pyridoxamine and its derivatives in the presence of different metal ions has been intensively studied.[4] Different approaches including chiral ligands,[5] chiral pyridoxamine derivatives,[6] polymeric,[7] dendrimeric pyridoxamines[8] as well as others[9] have been achieved, but to the best of our knowledge no catalytic enantioselective reaction has been developed until now.

We recently communicated the first attempts towards the catalytic and enantioselective formation of α-amino acid

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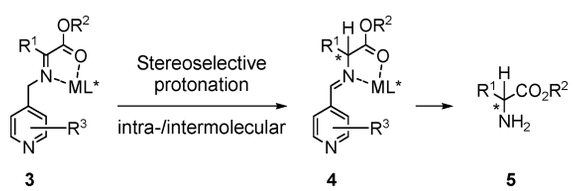
derivatives *via* half-transamination of α-keto esters in organic solvents with zinc(II) and copper(I)-bisoxazoline complexes.[10] This approach includes (chiral) Lewis acid catalysts to fix the reactants in the optimal geometry and to enhance the reactivity of the pyridoxamine. In the *in vivo* system, an enzyme controls the reaction course in a highly selective manner by binding the substrate and PLP in the optimal geometry. This is the main challenge in mimicking such systems.

In this paper we will disclose the development and mechanistic investigations of our attempts to mimic enzymatic transamination reactions by a catalytic enantioselective approach using chiral Lewis acids as catalysts for the reaction of α-keto esters with primary amines as the nitrogen source. The challenge we are facing is outlined in Scheme 2: First we have to control the formation of ketimine **3**, second to control, in a stereoselective manner, the formation of aldimine **4**, and finally the hydrolysis of **4** to release the optically active α-amino acid. Furthermore, we have to try to drive the half-transamination in the desired direction: ketimine to aldimine to α-amino acid. This [1,3]-proton-transfer in native or artificial systems has been extensively studied.[9] We will show that the half-transamination can be catalyzed by Lewis acid complexes (ML* in Scheme 2) and in order to develop a catalytic enantioselective approach, labelling studies, reaction condition and ligand screenings were performed. Finally, the catalytic enantioselective developments will be outlined and some mechanistic details discussed.

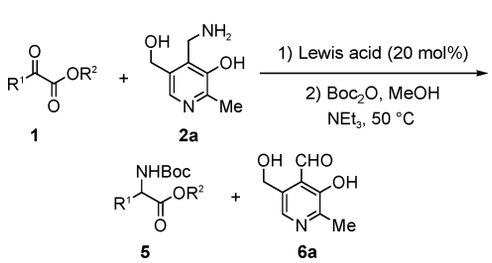


Scheme 2 The stereoselective induction in the asymmetric half-transamination is determined by the protonation of ketimine **3** giving aldimine **4**, which is hydrolyzed to the α-amino acid derivative **5**.

Results and discussion

Catalytic half-transaminations of α-keto esters

Different Lewis acids can catalyze the half-transamination of ethyl pyruvate **1a** with pyridoxamine **2a** (Scheme 3, R^1 = Me, R^2 = Et). The screening results are presented in Table 1.



Scheme 3 Half-transamination of different α-keto esters **1** with pyridoxamine **2a**.

Lewis acids, such as $Zn(OTf)_2$, $AlMe_3$, $InCl_3{\cdot}3H_2O$, $La(OTf)_3$ or $ZrCl_4$ can catalyze the half-transamination of ethyl pyruvate **1a** with pyridoxamine **2a** (Table 1, entries 1–5). Interestingly, it is possible to avoid the use of a metal Lewis acid catalyst since boron compounds such as boranes, borates or even boronic acid catalyze the half-transamination of **1a** in acceptable yields. We started testing boronic acid as the catalyst (20 mol%) and 38% yield of the Boc-protected alanine derivative **5a** was obtained (entry 6). Since it was not obvious if the catalytic activity of boronic acid is due to Lewis or Brønsted acidity, different boron compounds such as BEt_3, $B(OPh)_3$ and BCl_3 were tested. BEt_3 showed the same activity as $Zn(OTf)_2$ and 28% yield of **5a** was found (entry 7). To our surprise the yield of **5a** improved to 55% when 10 mol% of BEt_3 was used (entry 8). We believe that the presence of a higher amount of the boron compound deactivates either the substrate, the pyridoxamine or activates the reverse reaction. Furthermore, $B(OPh)_3$ was found to be an active catalyst and shows a comparable activity to BEt_3 and $Zn(OTf)_2$ under the same reaction conditions. BCl_3, the formally strongest Lewis acid among the boron compounds tested, gave 43% yield of **5a** (entry 10).

Table 1 Results of the Lewis-acid catalyzed half-transamination of ethyl pyruvate **1a** with pyridoxamine **2a**[a]

Entry	Catalyst	Yield[b]
1[c]	$Zn(OTf)_2$	28
2[c,d]	$AlMe_3$	35
3[c]	$InCl_3{\cdot}3H_2O$	37
4	$La(OTf)_3$	22
5	$ZrCl_4$	22
6	$B(OH)_3$	38
7	BEt_3	28
8[e]	BEt_3	55
9	$B(OPh)_3$	30
10	BCl_3	43

[a] For reaction conditions see Experimental Section. [b] Isolated yield after protection of the free amine with $(Boc)_2O$. [c] From reference 10. [d] Reaction performed in $MeNO_2$. [e] 10 mol% of the catalyst was used.

Table 2 Summary of the Lewis-acid mediated half-transamination of different pyruvate derivatives **1a**–**1g** with pyridoxamine **2a**[a]

Entry	Catalyst	R^1	R^2	Yield [%][b]
1	$Zn(OTf)_2$	Me	Et **1a**	**5a** 28
2	$Zn(OTf)_2$	CH_2*i*-Pr	Et **1b**	**5b** 6
3[c]	BEt_3	CH_2*i*-Pr	Et **1b**	**5b** 33
4[d]	$Zn(OTf)_2$	$(CH_2)_2C(H)=CH_2$	Et **1c**	**5c** 40
5	$Zn(OTf)_2$	CH_2-indole	Me **1d**	**5d** 19
6	$Zn(OTf)_2$	CF_3	Et **1e**	**5e** 0
7	$Zn(OTf)_2$	CH(Br)-CH_3	Et **1f**	**5f** 0
8	$Zn(OTf)_2$	Me	CH_2Ph **1g**	**5g** 15

[a] For reaction conditions see Experimental Section. [b] Isolated yield after protection of the free amine with $(Boc)_2O$. [c] 10 mol% of the catalyst was used. [d] No ligand-accelerating effect was observed as **7a** gives 40% yield as well.

The Lewis-acid transamination shows a ligand accelerating effect as *e.g.* Cu(I) and Ag(I) in combination with 1,2-diphenylphosphinoethane are efficient catalysts and up to 51% yield of **5a** was obtained.[10] For catalyst **7a**, a chiral Lewis acid (Fig. 2, *vide infra*), we also observed a ligand accelerating effect and the yield of **5a** was slightly improved compared to $Zn(OTf)_2$ as the catalyst.

The Lewis acids can catalyze the half-transamination of different alkyl-substituted (R^1 = CH_3 (**1a**), CH_2-*i*-Pr (**1b**), $(CH_2)_2$-C(H)=CH_2 (**1c**) or CH_2-indole (**1d**)) α-keto esters (Scheme 3). The yield of the corresponding Boc-protected α-amino ester is dependent on the substituents R^1 and R^2 and 6–40% yield of **5** were obtained with 20 mol% of $Zn(OTf)_2$ or 10 mol% of BEt_3 as the catalyst (Table 2, entries 1–5). The isopropyl derivative **1b** gives low yield of the corresponding Boc-protected α-amino ester **5b**, whereas the alkene-derived **1c** gives the best yield for the Zn(II)-catalyzed half-transamination in MeOH. As mentioned previously, the use of BEt_3 had a positive effect on the reaction yield and for **1b** as the substrate, an improvement to 33% yield for **5b** was obtained (entry 3). The yields of the corresponding Boc-protected α-amino esters are dependent on the steric bulk of the substituent on the α-keto function and only *n*-alkylated substrates gave acceptable yields, while for α-keto esters having a branched substituent a drop in reactivity was observed. Substrates having a CF_3 (**1e**) or CH(Br)-CH_3 (**1f**) substituent in α-position to the keto function were found to be

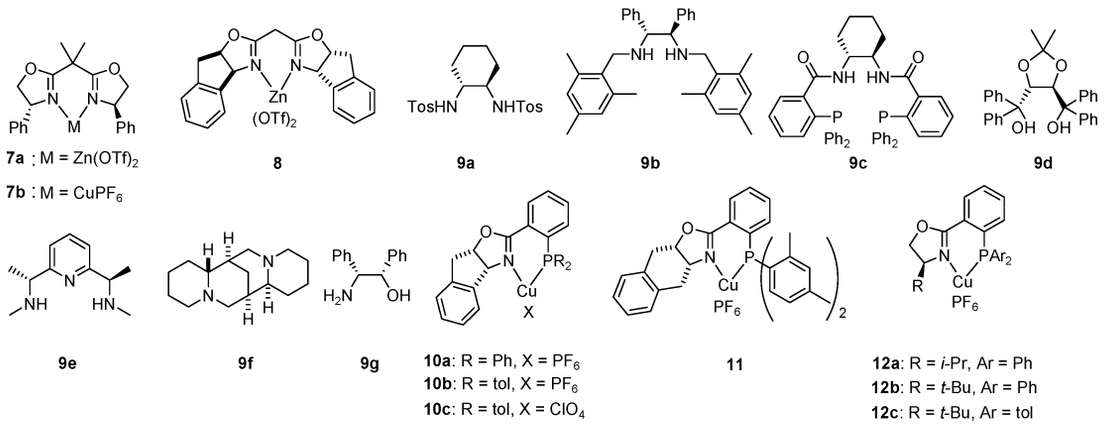


Fig. 2 Chiral catalysts for the half-transamination of α-keto esters.

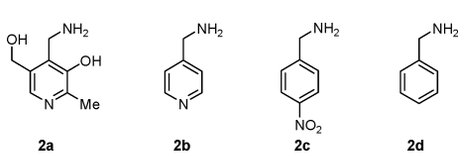
unreactive (*vide infra*, entries 6, 7). Larger ester functions in the substrate are also tolerated and for benzyl pyruvate **1g** 15% yield of **5g** was isolated (entry 8).

Mechanistic studies

In an attempt to obtain information about the reaction mechanism and intermediates, we have studied (*i*) the influence of different primary nitrogen sources and (*ii*) reactions in deuteurated solvents.

Different primary amine sources

Matsushima and Matsumoto,[4i] and Snell *et al.*[4e] have studied the influence of different primary amines as nitrogen sources in the Al(III)-mediated half-transamination of ethyl pyruvate and pyruvic acid in MeOH, respectively. They found that among pyridoxamine **2a**, 4-picolylamine **2b**, 3-hydroxy-4-picolylamine, 3-hydroxy pyridine and benzylamine, only the former was an active nitrogen source.[4i] Our observations under catalytic conditions are in accordance with these results as the testing of **2a**, **2b**, 4-nitro benzylamine **2c** and benzylamine **2d** (Scheme 4) as nitrogen sources in the Zn(II)-catalyzed transamination of **1a** in MeOH gave only the Boc-protected alanine derivative **5a** (28% yield) when using **2a**, while the other nitrogen sources were unreactive. This shows that for the transamination of **1a** by **2a** (*i*) the pyridine *N*-atom plays an important role probably acting as a proton acceptor and (*ii*) that the 3-hydroxy group is necessary for coordination to the metal center. However, to our surprise we have found that the half-transamination of **1a** by **2b** took place in MeOH using BEt_3 as the catalyst resulting in 9% yield of **5a**. This is, according to our knowledge, the first time that a nitrogen source having no substituent in the 3-position of the pyridine ring has been applied for the half-transamination reaction. The two other nitrogen sources, **2c** and **2d**, are not useful as donors for the BEt_3-catalyzed reactions. These findings could indicate that the boron-catalyzed transamination reaction follows a different mechanism compared to the Zn(II)-catalyzed reaction.



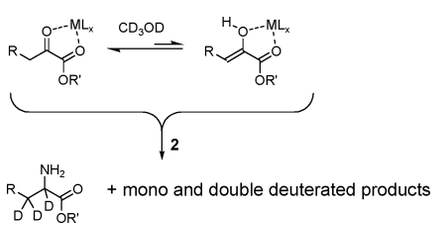
Scheme 4 Different nitrogen sources for the zinc(II) or boron(III) catalyzed half-transaminations of α-keto esters.

Snell *et al.* have also investigated the use of different nitro substituted salicylaldehydes for the reverse half-transamination reactions, *i.e.* the reaction following the opposite course to the one being currently under investigation.[4d,e] In contrast to our findings, they observed conversion in the Al(III)-mediated half-transaminations of glutamic acid or serine, applying 4-nitro- and 6-nitro salicylaldehyde. They showed that only the 2-formyl- and the 3-hydroxy group attached to the ring are necessary to obtain a reactive reverse half-transamination system.[4d,e]

We observed good catalytic activity in the Zn(II)-catalyzed transamination of methyl-3-indole pyruvate **1d** with 4-picolylamine **2b** in MeOH, where 66% isolated yield of the Boc-protected methyl tryptophan ester **5d** was obtained. This is in contrast to the transamination of **1d** with pyridoxamine **2a** which gives only 19% yield of **5d** for the Zn(II)-catalyzed reaction. This indicates that the half-transamination system using **2a** as the nitrogen source is less active compared to **2b** by a factor of *ca.* 3. It should also be noted that the other two nitrogen sources, **2c** and **2d**, were unreactive and no product was isolated, and therefore no further simplification of the system was possible.

Deuterium experiments

The half-transamination reaction of methyl-3-indole pyruvate **1e** with pyridoxamine **2a** catalyzed by $Zn(OTf)_2$ in CD_3OD gives three differently labelled products: mono-, double and triple deuterated Boc-protected methyl tryptophan ester **5d** were found in low yield (6%), according to MS and the spin system in the ^1H NMR spectrum. It is noteworthy that the reaction of **1d** with 4-picolylamine **2b** catalyzed by $Zn(OTf)_2$ in CD_3OD gives at least two differently labelled products in 16% isolated yield. In this case the mono-deuterated product was not detected, but double and triple deuterated derivatives were isolated. Interestingly, not only the expected position at the newly formed stereocenter showed incorporation of a deuterium atom, but also the CH_2-group in the α-position to the keto function, indicating that the enol is probably the reactive species (see Scheme 5).



Scheme 5 Proposed mechanism for deuterium incorporation to the product *via* enolisation of the substrate.

Based on the isolated yields we can compare the reaction rates for the two different nitrogen sources, pyridoxamine **2a** and 4-picolylamine **2b** in MeOH and CD_3OD. The half-transamination of methyl-3-indole pyruvate **1d** with **2a** in MeOH is approximately three times faster than in CD_3OD ($k_H/k_D \cong 3.2$), whereas for the reaction with **2b** an isotope effect of ~4 results ($k_H/k_D \cong 4.1$). It is notable that **2a** is less reactive in

Table 3 Influence of different solvents on the enantioselective half-transamination of methyl-3-indole pyruvate **1d** with **2b**[a]

Entry	Catalyst	Reaction time/h	Solvent	Yield [%][b]	Ee [%][c]
1[d]	**7a**	20	MeOH	50	*rac*
2	**7a**	40	*i*-PrOH	18	*rac*
3[d]	**7a**	40	$MeNO_2$	10	19 (*d*)
4	**7a**	40	$PrNO_2$	15	5 (*d*)
5	**7a**	40	Toluene	33	*rac*
6[d]	**7b**	40	$MeNO_2$	15	20 (*d*)
7	**7b**	40	THF	25	*rac*

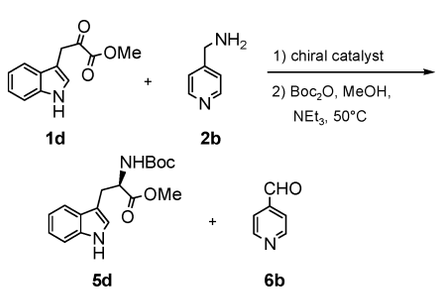
[a] For reaction conditions see Experimental Section. [b] Isolated yield after protection of the free amine with $(Boc)_2O$. [c] The enantiomeric excess was determined with a Chiralpak AS column. [d] From reference 10.

the half-transamination of **1d** than **2b**, because no successful application of the latter compound has been known until now. This could be an indication that different reaction mechanisms for the two nitrogen sources are operating. Notably, the reaction of ethyl pyruvate **1a** with **2a** catalyzed by $Zn(OTf)_2$ in CD_3OD afforded three differently deuterated products, as well as a mono deuterated species as the mainly isolated compound. This reaction is only a factor 0.7 ($k_H/k_D \cong 1.4$) slower in CD_3OD compared to the reaction in MeOH. These deuterium experiments indicate that although **1d**, both in the presence or absence of $Zn(OTf)_2$, is present in the keto form only in CD_3OD, it is the enol that is active during the reaction. The low amount of enol present in solution could be an explanation for the low yields found for this system. In *e.g.* $CDCl_3$ or $CHCl_3$, **1d** exists mainly in the enol, but the solvent is not protic enough to afford acceptable yields of the α-amino acid derivative (see Table 2).

Support for the enol of the α-keto ester being involved in the half-transamination reaction is obtained from attempts to aminate methyl-3-indole glyoxylate and ethyl phenylglyoxylate, where enolisation is impossible. Both compounds were found to be unreactive under the standard reaction conditions.

Catalytic enantioselective half-transaminations

Based on the observations mentioned above, our general interests in catalytic enantioselective reactions and the importance of these reactions, we have tried to apply this information for an asymmetric version of this reaction. Recently, we communicated the first example of a catalytic enantioselective half-transamination of methyl-3-indole pyruvate **1d** with Zn(II)- or Cu(I)-bisoxazoline catalysts in protic solvents.[10] For these systems the Boc-protected methyl tryptophan ester **5d** was formed in about 20% yield and up to 37% ee. Due to the higher reactivity of 4-picolylamine **2b** compared to pyridoxamine **2a**, we decided to do the further screening exclusively with **2b**. We have studied different factors including Lewis acids, solvents, ligands, counterions and additives for this reaction to improve yield and enantioselectivity (Scheme 6).



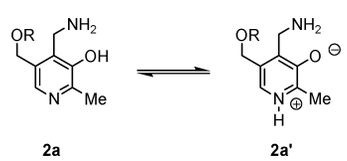
Scheme 6 Catalytic, enantioselective half-transamination of methyl-3-indole pyruvate **1d** with 4-picolylamine **2b**.

Influence of the solvent

The first factor investigated was the influence of the solvent. The screening of a variety of protic and aprotic solvents in the reaction of methyl-3-indole pyruvate **1d** with 4-picolylamine **2b** in the presence of the chiral bisoxazoline catalysts **7a**,**b** (Fig. 2) are given in Table 3. The results in Table 3 indicate that the pK_a-value of the solvent affects enantioselectivity and yield of the reaction. In nitroalkanes the yields are generally lower compared to alcohols, but $MeNO_2$ is the best solvent regarding the enantiomeric excess (entries 1–4). On the other hand we were very surprised to find that the half-transamination reactions can also proceeds in aprotic solvents such as toluene, $CHCl_3$ and THF, and the relatively high yields obtained of **5d** in toluene and THF are astonishing (entries 5,7). The reaction can also be performed in *t*-BuOH, 1,2-dimethoxy ethane and *N,N*-dimethyl formamide affording low yields (<10%) and racemic products. However, in $CHCl_3$ only 8% ee of **5d** was obtained and the product was formed with the opposite absolute configuration compared to the reactions performed in $MeNO_2$.[11]

The screening shows that the solvent has an important influence on yield and enantioselectivity and it should be noted that enantioselectivity is observed only in combination with low yields of the Boc-protected α-amino acid derivative. If the reaction is performed in a solvent that gives acceptable yield the product is formed as a racemate. One important fact to mention is that independent of the solubility of the substrate in the particular solvent, a slurry appears after the addition of the primary amine (**2b**) which is constantly present throughout the reaction. The low solubility might be responsible for the poor yields. Only in DMF was a homogenous solution observed.

Recently Wong and Kiruba reported a theoretical study concerning the different tautomeric forms of vitamin-B_6 derivatives in different solvents.[12] In accordance with our experimental findings, they reported that the zwitterionic form (**2a′**) predominates in polar solvents, whereas the neutral form is dominant in apolar solvents (Scheme 7).



Scheme 7 Tautomerism model for pyridoxamine **2a**.

This tautomerism is not apparent for 4-picolylamine **2b**, where only the pyridine *N*-atom can be protonated. Anyway, the lack of formation of this protonated form, or the lower solubility of this intermediate in less polar solvents could explain the lower reactivity for the half-transamination in less polar solvents. We know that especially the pyridine *N*-atom is important for the reaction, since no product was found with benzylamine or 4-nitro benzylamine as the nitrogen sources and thus the protonation of the pyridine *N*-atom and the formation of an ionic intermediate are important for the half-transamination reaction to take place. However, the relatively high yield in toluene (33%), a classic apolar solvent where the neutral form should be predominant, can not be explained by this tautomerisation model. Therefore, we suggest that different mechanisms are in operation when using the nitrogen sources pyridoxamine or 4-picolylamine.

Table 4 Results of the half-transamination of methyl-3-indole pyruvate **1d** with 4-picolylamine **2b** catalyzed by Cu(I)–P–N catalysts[a]

Entry	Catalyst	Reaction time/h	Yield [%][b]	Ee [%][c]
1	**10a**	40	10	14 (*d*)
2	**10b**	40	13	46 (*d*)
3[d]	**10b**	80	10	38 (*d*)
4[e]	**10b**	40	18	10 (*d*)
5	**10c**	40	9	17 (*d*)
6	**11**	40	11	11 (*d*)
7	**12a**	40	16	18 (*l*)
8	**12b**	20	16	6 (*l*)
9	**12c**	40	10	14 (*l*)

[a] For reaction conditions see Experimental Section. [b] Isolated yield after protection of the free amine with $(Boc)_2O$. [c] The enantiomeric excess was determined with a Chiralpak AS column. [d] Reaction performed at 0 °C. [e] Reaction performed in toluene as the solvent.

Additives

Different additives such as HFIP (1,1,1,3,3,3-hexafluoroisopropanol), ethylene glycol, NEt_3 and silica were tested for their influence on the reaction (yield and selectivity). In contrast to the half-transamination of ethyl pyruvate **1a** with pyridoxamine **2a**, where HFIP had no influence on the reaction yield,[9] the reactivity could be improved for the half-transamination of methyl-3-indole pyruvate **1d** with 4-picolylamine **2b** catalyzed by **7a** and 38% yield of the Boc-protected methyl tryptophan ester **5d** was obtained. The use of HFIP has a positive effect on the yield of **5d**, but unfortunately no enantiomeric excess was formed for the isolated product, whereas the reaction without HFIP gave 19% ee. The use of NEt_3 in toluene did not give any improvement of yield or ee (20% yield of racemate). However, performing the half-transamination reaction catalyzed by **7b** in THF with 20 mol% of NEt_3 improved the yield of **5d** to 34%, whereas the analogous reaction catalyzed by **7a** gave no improvement compared to the reaction in THF in the absence of additives and the product was formed as a racemate. In the experiments applying ethylene glycol as the co-solvent (1 : 1 mixture of $MeNO_2$: ethylene glycol) and applying catalyst **8** (Fig. 2) product **5d** was formed in 19% yield and 8% ee and, most notably, with the opposite absolute configuration compared to the one observed in the absence of an additive.

In general, additives have a negative effect on the enantioselectivity and only HFIP in $MeNO_2$ and NEt_3 in THF in combination with **7a** or **7b** as the catalyst are able to improve the yield.

Chiral catalysts

The chiral ligands/catalysts shown in Fig. 2 were tested for the catalytic enantioselective half-transamination of methyl-3-indole pyruvate **1d** with 4-picolylamine **2b**.

Unfortunately, none of the ligands **9a**–**9g** in combination with *e.g.* Cu(I)- or Zn(II)-induced enantioselectivity in the half-transamination reaction. Bernauer *et al.* reported an enantioselective half-transamination of phenyl pyruvic acid with a Cu(II)-ligand **9e** complex (using 5 equiv. of **9e**!) giving up to 54% ee (measured by circular dichroism) for the alanine derivative in a buffered aqueous solution.[5] It was therefore surprising for us that we did not observe any enantioselectivity for the Cu(I)-[13] or Zn(II)-catalyzed half-transamination of methyl-3-indole pyruvate **1d** in MeOH or $MeNO_2$ using **9e** as the chiral ligand. A crucial fact for a successful half-transamination in the present system seems to be an imine-functionality in the ligand, and amine or amide functionalities are not tolerated if enantioselectivity should be obtained.

However, it is well known that Cu(I) is a good Lewis acid for (chiral) P–N ligands[14] and we therefore turned our attention to P–N ligands (**10**–**12**). To our delight we found that several of the P–N–Cu(I) complexes were able to induce enantioselectivity in the reaction using **1d** as the substrate. In the course of our screening we find now that the enantioselectivity obtained with the catalysts **10**–**12** shown in Fig. 2 is dependent on three factors: (*i*) the steric bulk at the substituents on the phosphorus atom, (*ii*) the steric demand of the oxazoline moiety and (*iii*) the coordination properties of the counterion. The isolated yield of **5d** obtained in $MeNO_2$ was generally low and varied in a range from 10–20%. Catalyst **10b** having the indane moiety at the oxazoline and two tolyl functions at the phosphorus atom turned out to be the best chiral complex giving 46% ee for **5d** (Table 4, entry 2). The enantioselectivity drastically drops when the steric bulk on the phosphorus part is reduced to phenyl groups (catalyst **10a**) instead of tolyl (catalyst **10b**) (entry 1 *vs.* 2), or if a stronger coordinating counterion, such as ClO_4^- instead of PF_6^- (catalyst **10c**) is used (entry 5 *vs.* 2). This indicates that stronger coordinating ions or solvents may distort the optimal geometry of the intermediate/transition state and therefore face-shielding is lowered, resulting in reduced enantioselectivities.

Decreasing the reaction temperature to 0 °C lowered the enantiomeric excess of adduct **5d** to 38% ee (entry 3). However, it is important to note that enantioselectivity, although low (10% ee) can also be obtained with **10b** as the catalyst in toluene (entry 4). This is the first time we have observed an asymmetric induction in an aprotic solvent.

The third factor affecting the enantioselectivity is the size of the oxazoline moiety. For this part of the chiral ligand, the trend is inverted compared to the phosphorus part. An enlargement of the steric bulk on the oxazoline by an additional CH_2-group in the ring next to the oxazoline portion (ligand **11**) has a negative effect on the enantiomeric excess and only 11% ee was observed of the Boc-protected methyl tryptophan ester **5d** (entry 6) compared to 46% ee when catalyst **10b** is used. The indane moiety seems to be optimal for this half-transamination, as not only the increase of steric bulk, but also the introduction of *i*-Pr or *t*-Bu substituents on the oxazoline ring affects the enantioselectivity in a negative manner (catalysts **12a**–**c**, entries 7–9).

It is notable that B(III) and Al(III) complexes which turned out to be effective catalysts for different half-transamination reactions, in combination with chiral ligands induced no enantioselectivity for this reaction.

Conclusion

We have shown that Lewis acid catalysts can promote the transamination of α-keto esters with different nitrogen sources in protic solvents. For the linear alkylated α-keto esters, boron compounds in MeOH can catalyze the reaction to an acceptable level. Enantioselectivity in the reaction is dependent on several factors: (*i*) the pK_a of the solvent, (*ii*) the coordination properties of counterion or solvents and (*iii*) the optimal geometry of the transition state determined by the structure of the catalyst. We have found that chiral Cu(I)–P–N complexes are the best catalysts for the enantioselective reactions. Interestingly different nitrogen sources could be applied for this reaction type and the reaction proceeds even in aprotic solvents such as toluene.

Experimental section

General

The ^1H and ^{13}C NMR spectra were measured on a Varian Mercury spectrometer at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield from $CHCl_3$ (δ = 7.26) for ^1H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0) for ^{13}C NMR. All solvents used were of p.a. quality and were dried according to standard procedures.

Flash chromatography (FC) was carried out using Merck silica gel 60 (230–400 mesh). The ee was determined by HPLC using a Chiralpak AS column with *i*-PrOH/hexane as eluent. All catalytic reactions were carried out under an atmosphere of N_2 or Ar.

Materials

All commercially available compounds were used without any further purification. 2,2′-Isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline], $TMSCHN_2$ (2.0 M in hexane), 4-picolylamine, pyridoxamine dihydrochloride hydrate, ethyl pyruvate, indole-3-pyruvic acid, BEt_3, $B(OH)_3$, BCl_3, $B(OPh)_3$, $Zn(OTf)_2$, $[Cu(I)(CH_3CN)_4]PF_6$ and the ligands **9f** and **9g** were purchased from Aldrich. The indane-derived ligand and its Zn(II) complex **8** were synthesised according to a literature method.[15] Ligand **9c** was purchased from Strem Chemicals, whereas the ligands **9a**,[16] **9b**,[17] **9d**[18] and **9e**[5] were synthesised according to literature methods. The P–N ligands and the corresponding Cu(I) complexes were synthesised according to described methods.[19]

General procedure for the catalytic (enantioselective) transamination of α-keto esters

The Lewis acid (0.1 mmol, 20 mol% *versus* the nitrogen source) and the chiral ligand (0.11 mmol, 22 mol%) were stirred for 30 min under vacuum. Then 2 ml of solvent was added and the solution was stirred for 1 h before the nitrogen source (0.5 mmol) and the α-keto ester (1 mmol, 2 eq.) were added. The resulting mixture was stirred for 20 h and hydrolysed by the addition of H_2O (2 eq.) and CF_3COOH (1 eq.). The free amino group was protected by adding NEt_3 (210 μl, 3 eq.) and $(Boc)_2O$ (218 mg, 2 eq.) to the MeOH solution and stirred for 30 min at 50 °C.[20] After cooling the mixture to ambient temperature the solvent was removed and the oily residue was purified by FC using CH_2Cl_2/Et_2O 9 : 1 as eluent. The purity of the products was checked by ^{1}H NMR and TOF MS and the values of the known compounds **5a**,[21] **5e**[22] and **5h**[21] were compared with the products described in the literature.

Ethyl *N*-*tert*-butyloxycarbonyl-2-amino-4-methyl-pentanoate 5b

^{1}H NMR ($CDCl_3$): δ 4.89 (br d, 1H, J = 8.4 Hz, N*H*), 4.28 (m, 1H, C*H*), 4.18 (q, 1H, J = 6.8 and 14.0 Hz, OCH_2), 1.69 (m, 1H, CH_2), 1.59 (m, 1H, CH_2), 1.48 (m, 1H, $CH(CH_3)_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.27 (t, 3H, J = 7.6 Hz, CH_3), 0.94 (d, 3H, J = 3.2 Hz, CH_3), 0.93 (d, 3H; J = 3.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 173.5, 155.4, 79.7, 61.1, 52.1, 41.9, 28.3, 24.8, 22.8, 21.9, 14.1; HRMS (ES$^+$ TOF) calcd for $C_{13}H_{25}NO_4$ [M + Na]$^+$ 282.1681, found 282.1679.

Ethyl *N*-*tert*-butyloxycarbonyl-2-amino-5-hexenoate 5c

^{1}H NMR ($CDCl_3$): δ 5.77 (m, 1H, C(*H*)=CH_2), 5.02 (m, 3H, CH=CH_2 and N*H*), 4.28 (dd, 1H, J = 8.0 and 13.2 Hz, C*H*), 4.18 (q, 2H, J = 6.8 and 14.4 Hz, OCH_2), 2.12 (m, 2H, CH_2), 1.90 (m, 1H, CH_2), 1.71 (m, 1H, CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.27 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 172.8, 155.3, 137.0, 115.6, 79.8, 61.3, 53.0, 32.0, 29.4, 14.1; HRMS (ES$^+$ TOF) calcd for $C_{13}H_{23}NO_4$ [M + Na]$^+$ 280.1525, found 280.1529.

N-(*tert*-Butyloxycarbonyl)-2-(3-indolyl)glycin-methylester 5d

The ee was determined by HPLC on a Chiralpak AS column with hexane/*i*-PrOH 80:20 as eluent. R_t (min), 5.7 (*d*-isomer), 7.3 (*l*-isomer). The absolute configuration was assigned by comparison with a commercially available sample of (*l*)-tryptophan that has been derivatised to the Boc-protected tryptophan methylester.

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