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# Catalytic enantioselective transaminiation of α-keto esters: an organic approach to enzymatic reactions

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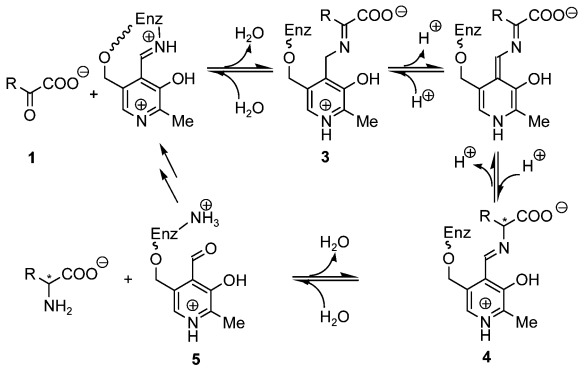
**The half-transamination reaction of α-keto esters with pyridoxamine or 4-picolylamine was found to be catalysed by different metal catalysts in organic solvents giving moderate yields and enantioselectivities of up to 37% ee for methyl-3-indole pyruvate.**

The development of biomimetic reactions is one of the major challenges for synthetic chemists. These reactions are generally very complicated and the mechanisms are often only partly elucidated. Therefore an approach dealing with classical organic or organometallic chemistry is challenging.

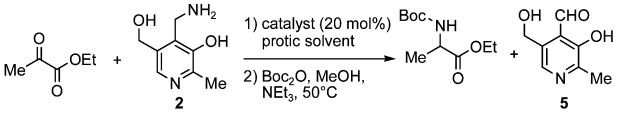
The biological transamination of α-keto acids to give α-amino acids is catalysed by the vitamin $B_6$-dependent amino-transferase, and proceeds *via* several protonation/isomerisation steps going from the ketimine **3** to the aldimine **4** (Scheme 1).[1]



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

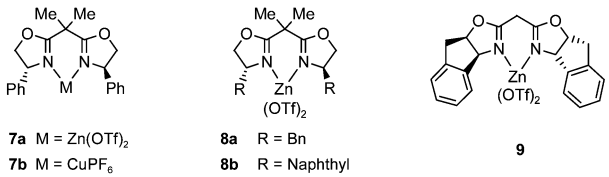
The mechanism of the transamination of α-keto acids with pyridoxamine to give α-amino acids (or the reversed reaction) in the presence of stoichiometric amounts of different metal ions has been intensively studied.[2] Different approaches have been investigated, including chiral versions,[3] however, to the best of our knowledge no catalytic and enantioselective method has been presented up until now.

We present here the first catalytic† and enantioselective half-transamination[1c] reaction of α-keto esters and pyridoxamine or 4-picolylamine, based on (chiral) Lewis acid catalysts to activate the pyruvate derivatives and protic solvents, such as $CH_3OH$ or $CH_3NO_2$, as a proton source for the isomerisation steps. For the first time isolated yields of the α-amino acid derivatives are given, whereas most of the known half-transaminations are based on kinetic studies of reaction rates.[2,4] The half-transamination of α-keto esters with pyridoxamine derivatives is a reversible process and therefore in an equilibrium with the reverse reaction (half-transamination of the α-amino acids with pyridoxal **5**). Hence high reaction yields and enantioselectivities are difficult to achieve. Despite this fact different metal salts, such as $Zn(OTf)_2$, $CuPF_6{\cdot}4CH_3CN$, AgOTf, $AlMe_3$ or $InCl_3{\cdot}3H_2O$ (see Table 1) are able to catalyse the half-transamination of ethyl pyruvate with pyridoxamine **2** in protic solvents (Scheme 2).



**Scheme 2** Half-transamination of ethyl pyruvate with pyridoxamine **2**.

We observe a moderate ligand accelerating effect for this reaction if catalyst **7a** (Fig. 1) is used, and 37% of the Boc-protected alanine derivative was isolated (Table 1, entry 3) compared to the reaction with $Zn(OTf)_2$ as catalyst where a 28% yield was found (entry 2) and in the absence of a catalyst (entry 1) where very low conversion was found.



**7a** M = $Zn(OTf)_2$
**7b** M = $CuPF_6$
**8a** R = Bn
**8b** R = Naphthyl
**9**

**Fig. 1** Suitable chiral catalysts for asymmetric half-transamination reactions.

The change from $CH_3OH$ to a solvent with a higher p$K_a$ such as $CH_3NO_2$ does not affect the yield (40%, entry 4). It is well known that additives such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) can promote the release of the product from the catalyst,[5] but no effect of *e.g.* HFIP (20 mol%) on the reaction yield was found (entry 5).

A higher activity for this transamination was detected when the reaction temperature was increased to 50 °C (66% yield, entry 6). Interestingly Cu(II) does not catalyse the reaction (entry 7), but Cu(I), Ag(I), Al(III) and In(III) are active Lewis acid catalysts for this kind of transformation, giving up to 51% yield for Cu(I) in combination with dppe (1,2-diphenylphosphinoethane) (entries 8–11). A reasonable explanation for the unreactivity of Cu(II) could be the electron configuration at the metal centre. The unreactive Cu(II) has a $d^9$ configuration,

**Table 1** Results of the metal catalysed half-transamination of ethyl pyruvate with pyridoxamine **2**

| Entry | Catalyst | *T*/°C | Solvent | Yield (%) [a] |
|---|---|---|---|---|
| 1 | — | RT | MeOH | 0 |
| 2 | $Zn(OTf)_2$ | RT | MeOH | 28 |
| 3[b] | **7a** | RT | MeOH | 37 |
| 4[b] | **7a** | RT | $MeNO_2$ | 40 |
| 5[b,c] | **7a** | RT | MeOH | 41 |
| 6[b] | **7a** | 50 | MeOH | 66 |
| 7 | $Cu(OTf)_2$ | RT | MeOH | 0 |
| 8 | $[Cu(dppe)]PF_6$ | RT | MeOH | 51 |
| 9 | [Ag(dppe)]OTf | RT | MeOH | 49 |
| 10 | $AlMe_3$ | RT | $MeNO_2$ | 35 |
| 11 | $InCl_3{\cdot}3H_2O$ | RT | MeOH | 37 |

[a] Isolated yield after protection of the free amine with $(Boc)_2O$. [b] Due to the low UV-absorbance of the product and the fragmentation under mild GC separation conditions, the enantiomeric excess could not be determined. [c] 20 mol% 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as additive.

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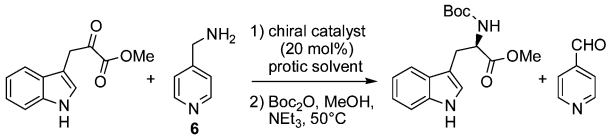
whereas all transamination catalysts, with the exception of Al(III), are isolelectronic and possess a $d^{10}$ configuration at the metal centre.

Changing from ethyl pyruvate to methyl-3-indole pyruvate the reactivity in $CH_3OH$ was low and only 19% of the product was isolated. Surprisingly, the use of 4-picolylamine **6** as amine source instead of pyridoxamine **2** (Scheme 3) gave good yields (Table 2, entry 1) whereas **6** was unreactive in combination with ethyl pyruvate. The pyridine N-atom has an important role during the isomerisation steps since benzylamine was unreactive under the standard reaction conditions.




**Scheme 3** Half-transamination of 3-methyl-indole pyruvate with 4-picolylamine and different (chiral) Lewis acid catalysts.

Matsushima and Matsumoto tried to use **6** in the transamination of pyruvic acid, but no conversion was observed.[2g] Therefore this is the first report of a transamination of a pyruvate derivative with **6** as the amine source, however, with a variety of different chiral catalysts no enantioselectivity could be induced with $CH_3OH$ being the solvent.

To our delight, we have found that in a solvent with a higher p$K_a$ than $CH_3OH$, such as $CH_3NO_2$, enantioselectivity can be induced with several chiral Lewis acid catalysts (see Table 2).

By changing the solvent from $CH_3OH$ to $CH_3NO_2$ 19% ee was found for the tryptophan derivative using **7a** as the catalyst (Table 2, entry 3). The change of solvent has a positive effect on the enantioselectivity, but in general poor yields are obtained in $CH_3NO_2$. With catalyst **7b** where Cu(I) is the central atom the same enantioselectivity was found as with **7a** (20% ee, entry 4). Modifying the R group from Ph (**7a**) to Bn (**8a**) in the oxazoline ring of the ligands shows a significant influence on the enantioselectivity and the product with **8a** as the catalyst was racemic (entry 5). With the bulky 1-naphthyl group at the oxazoline moiety the enantioselectivity is improved to 27% ee (entry 6). The most selective catalyst for the enantioselective transamination of methyl-3-indole pyruvate with **6** is catalyst **9**, having an indole substituent (Fig. 1). This catalyst gives 37% ee (entry 7), the highest enantioselectivity we observed up until now for this type of reaction.

In general enantioselectivity is observed only in combination with low yields. This fact can be a consequence of the equilibrium between the two half-transamination reactions we are dealing with, as mentioned above.

**Table 2** Summary of the metal catalysed half-transamination of methyl-3-indole pyruvate with 4-picolylamine **6**

| Entry | Catalyst | *t*/h | Solvent | Yield (%)[a] | Ee (%)[b] |
|---|---|---|---|---|---|
| 1 | $Zn(OTf)_2$ | 20 | MeOH | 66 | — |
| 2 | **7a** | 20 | MeOH | 50 | Rac |
| 3 | **7a** | 20 | $MeNO_2$ | 10 | 19 (D) |
| 4 | **7b** | 40 | $MeNO_2$ | 15 | 20 (D) |
| 5 | **8a** | 40 | $MeNO_2$ | 36 | Rac |
| 6 | **8b** | 40 | $MeNO_2$ | 22 | 27 (D) |
| 7 | **9** | 40 | $MeNO_2$ | 15 | 37 (D) |

[a] Isolated yield after protection of the free amine with $(Boc)_2O$. [b] The enantiomeric excess was determined by HPLC using a Chiralpak AS column.

We suggest that the p$K_a$ of the solvent and the geometry of the metal intermediate are the key factors to obtain enantioselective reactions. As soon as a distortion of the optimal geometry of the intermediate occurs, due to coordination of the solvent or other factors, the selectivity is diminished. In our further investigations we will try to find an ideal catalytic system with the help of molecular modelling to improve the enantioselectivity and reaction yields in parallel.

In summary, a new catalytic and enantioselective approach to chiral α-amino acids has been developed using Cu(I) or Zn(II) Lewis acid catalysts in combination with different chiral ligands. The reaction gives optically active alanine and tryptophan derivatives in low to moderate yields with low enantioselectivities. The enantiomeric excess shows a moderate dependency on the size of the functionality on the bisoxazoline rings of the ligands. Enantioselectivities can only be obtained when solvents with high p$K_a$ values, such as $CH_3NO_2$ are used, indicating that the protonation step is probably the key factor to obtain enantioselectivity. The improvement of the enantioselectivity in combination with good reaction yields will be the object of future studies.

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## Notes and references

† *Typical catalytic procedure*: The metal salt (0.1 mmol, 20 mol% *versus* the amine source) and the (chiral) ligand (0.11 mmol, 22 mol%) were stirred for 30 min under vaccum. Then 2 ml of solvent were added and the solution was stirred for 1 h before the amine source (**2** or **6**, 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 water (2 eq.) and trifluoroacetic acid (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 methanol solution and stirring for 30 min at 50 °C. After cooling the mixture to room temperature the solvent was removed and the oily residue was purified by FC using $CH_2Cl_2/Et_2O$ (9 : 1) as eluent. The enantiomeric excess 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 comparision with a commercially available sample of (L)-tryptophan that had been derivatised to the Boc-protected tryptophan methylester.


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