presented. Even under ambient conditions, the reaction gives optically active β-nitro-α-amino esters with excellent diastereo- and enantioselectivity.

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[11] A series of different N-protected α-imino esters were tested for the reaction and it was found that the *N*-(*p*-methoxyphenyl)-α-imino ester **1** led to a stable product as α-imino esters that have electron-withdrawing substituents at the nitrogen atom gave products which tended to decompose during workup.

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Catalytic Asymmetric Direct Mannich Reactions of Carbonyl Compounds with α-Imino Esters**

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The Mannich reaction is an important class of C–C bond-forming reactions in organic chemistry.[1] A number of methods for the diastereoselective reaction of imines with enolates has been reported,[1a, 2] and recently the first examples of catalytic enantioselective addition of enolates to imines were reported.[1c, 3] One disadvantage of these stereoselective Mannich reactions is the preparation and stability of the enolate, and a major step forward for this important class of reactions would be a catalytic enantioselective version that uses carbonyl compounds rather than the enolates.[4]

Recently, we demonstrated that simple chiral Lewis acids such as the bisoxazoline (BOX)–Cu^{II} complexes[5] can mimic aldolase enzymes, and a highly enantioselective homo-aldol reaction of pyruvate which gave diethyl-2-hydroxy-2-methyl-4-oxo-gluterate in up to 96% *ee* was developed.[6] In this homo-aldol reaction, the chiral Lewis acid acts both as a catalyst for the in situ generation/stabilization of the enol-pyruvate from pyruvate, and as a catalyst for the enantioselective addition step. This new aspect of Lewis-acid catalysis led us to try to develop other reactions based on this concept.

Herein we present the first catalytic diastereo- and enantioselective Mannich reaction of activated carbonyl compounds **1** with the α-imino ester **2** catalyzed by chiral Lewis acids (Scheme 1). This new development leads to a simple synthetic procedure for the formation of optically active highly functionalized α-amino acid derivatives **3** by using readily available carbonyl compounds rather than the often troublesome silyl enol ethers or silyl ketene acetals.

The reaction between ethyl pyruvate **1a** (R = H) and *N*-tosyl-α-imino ester **2** has been used for screening the reaction conditions for the chiral Lewis-acid catalyzed direct Mannich reaction. The metal ion is crucial for the success of this reaction. It has been found that copper(II) possesses the properties necessary for both the in situ generation of the enol species from **1a** and, in combination with chiral C_2-symmetric ligands, the stereoselectivity of the reaction. Table 1 presents some results for the reaction of **1a** with **2** in the presence of bisoxazolines and BINAP (2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) as chiral ligands. The use of the *t*Bu-BOX-$Cu(OTf)_2$ catalyst (*S*)-**4** in CH_2Cl_2 led to the formation of the Mannich adduct **3a** (R = H) in reasonable yield and 33% *ee* (Table 1, entry 1), whereas the di-Ph-BOX-$Cu(OTf)_2$ catalyst

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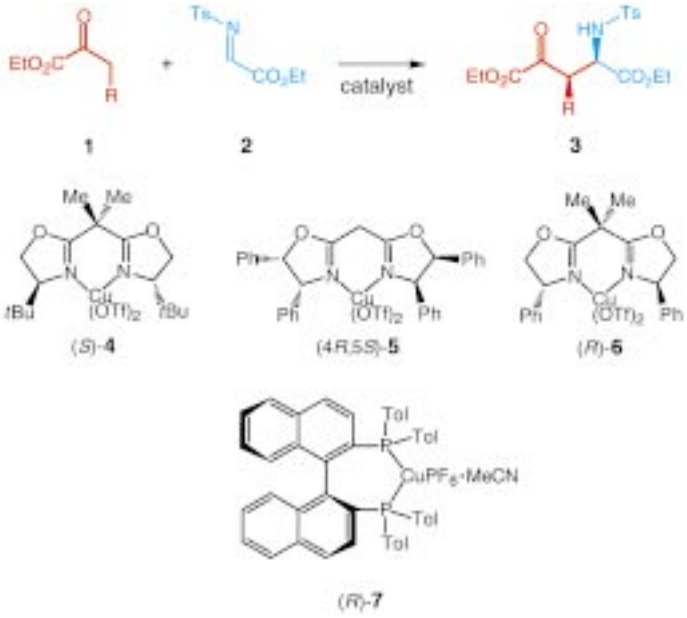

Scheme 1. Diastereo- and enantioselective Mannich reaction of activated carbonyl compounds **1** with α-imino ester **2**, catalyzed by chiral Lewis acids **4**–**7**. **1a**, **3a**: R = H; **1b**, **3b**: R = CH_3; **1c**, **3c**: R = Bn (Bn = Benzyl); **1d**, **3d**: R = Br.

Table 1. Catalytic enantioselective Mannich reaction of ethyl pyruvate **1a** (R = H) with *N*-tosyl-α-imino ester **2** using different catalysts under various reaction conditions.[a]

Entry	Catalyst	Solvent	t [h]	Yield [%][b]	*ee* [%][c]
1	(*S*)-**4**	CH_2Cl_2	40	76	33
2	(4*R*,5*S*)-**5**	CH_2Cl_2	40	44	12
3	(4*R*,5*S*)-**5**	THF	16	16	33
4	(*R*)-**6**	CH_2Cl_2	40	70	89
5	(*R*)-**6**	THF	16	45	76
6	(*R*)-**6**	Et_2O	40	< 5	–
7	(*R*)-**7**	CH_2Cl_2	40	< 10	–

[a] Experimental conditions: The reactions were performed with 0.25 mmol of **1a** and 0.375 mmol of **2**, and with 10 mol% catalyst. For further details see Supporting Information. [b] Yield of isolated product. [c] Enantiomeric excesses were determined by HPLC.

(4*R*,5*S*)-**5** gave lower yields and enantiomeric excesses of **3a** in CH_2Cl_2 and THF (Table 1, entries 2, 3). The application of the Ph-BOX-Cu(OTf)$_2$ catalyst (*R*)-**6** in the reaction was much more successful and led to **3a** in good yield and up to 89% *ee* (Table 1, entries 4, 5). However, catalyst (*R*)-**6** is solvent dependent, as < 10% of **3a** was obtained in Et_2O (Table 1, entry 6). The BINAP–Cu^I catalyst (*R*)-**7**, which has been successfully applied as a catalyst in several different types of addition reactions to **2**,[3d,e, 7] gave only traces of **3a** in the present reaction (Table 1, entry 7).

The combination of copper(II) and the Ph-BOX-ligand turned out to be an excellent catalyst for the Mannich reaction of α-carbonyl esters **1a**–**d** with the *N*-tosyl-α-imino ester **2**. The reactions proceeded in good yield, high *syn* selectivity, and excellent enantioselectivity. The best result for the reaction of ethyl pyruvate **1a** with **2** catalyzed by (*R*)-**6** is shown in Table 2, entry 1. Ethyl 2-oxo-butyrate **1b** reacts with **2** to give **3b** in 89% yield and excellent enantioselectivity (> 98%) of the *syn* diastereomer when (*R*)-**6** was used as the catalyst in CH_2Cl_2 (Table 2, entry 2). A decrease in the catalyst loading to 5 mol% improved the yield to 98%, with the same high diastereo- and enantioselectivity (Table 2, entry 3). The reaction can also be performed in THF with similar results (Table 2, entry 4). The application of catalyst (4*R*,5*S*)-**5** to the reaction of **1b** with **2** gave a slightly lower yield of **3b**; however, the Mannich adduct was obtained with good enantioselectivity (Table 2, entry 5). The reaction of the benzyl compound **1c** with **2** is sluggish at room temperature. However, the Mannich adduct **3c** was obtained in 94% yield with 97% *ee* of the major diastereomer when the reaction mixture was heated to 40 °C (Table 2, entry 6). Ethyl bromopyruvate **1d** reacts with **2** to give the Mannich adduct **3d** in good yield and enantioselectivity (Table 2, entry 7).

Table 2. Catalytic diastereo- and enantioselective Mannich reaction of a series of different α-carbonyl esters **1a**–**d** with *N*-tosyl-α-imino ester **2** (see Scheme 1).

Entry	Catalyst	R	Solvent	t [h]	Yield [%][a]	dr[b]	*ee* [%][c]
1	(*R*)-**6**	H (**1a**)	CH_2Cl_2	40	70 (**3a**)	–	89
2	(*R*)-**6**	Me (**1b**)	CH_2Cl_2	40	89 (**3b**)	> 10:1	> 98/ > 90
3	(*R*)-**6**[d]	Me (**1b**)	CH_2Cl_2	40	98 (**3b**)	> 10:1	94/ > 90
4	(*R*)-**6**	Me (**1b**)	THF	40	71 (**3b**)	> 10:1	91/69
5	(4*R*,5*S*)-**5**	Me (**1b**)	CH_2Cl_2	40	58 (**3b**)	> 10:1	63/29
6	(*R*)-**6**	Bn (**1c**)	CH_2Cl_2[e]	40	94 (**3c**)	> 10:1	97/-
7[f]	(*R*)-**6**	Br (**1d**)	CH_2Cl_2	20	79 (**3d**)	3:1[g]	78[h]

[a] Yield of isolated product. [b] Diastereomeric ratio measured by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Enantiomeric excesses were determined by HPLC. [d] 5 mol% of catalyst applied. [e] Reaction temperature 40 °C. [f] 2 Equiv of the *N*-tosyl-α-imino ester **2** used. [g] A 1:1 diastereomeric ratio was obtained after flash chromatography. [h] Enantiomeric excess measured after dehalogenation.

The results in Table 2 show the scope of the reaction; the Mannich reaction of different α-carbonyl esters gives highly functionalized 4-oxo-glutamic acid ester derivatives in high yield and diastereoselectivity, and with excellent enantioselectivity. Different substituents can be attached to the α-carbonyl functionality, for example, the presence of bromine allow for further functionalization at this position. Some epimerization occurs at the stereogenic center C3, to which the substituent is attached, during purification by flash chromatography. This problem can be overcome by a direct reduction of the 4-oxo functionality (see below).

Herein we present further potential applications of this new Mannich reaction: preparation of highly functionalized optically pure lactones by selective reduction of the 4-oxo functionality and removal of the *N*-tosyl substituent.

The Mannich adducts **3b**,**c** underwent a diastereoselective reduction of the 4-oxo functionality with L-selectride to give a mixture of the corresponding alcohols and lactones and treatment of the reaction mixture with PTSA (*p*-toluenesulfonic acid) led to the smooth formation of the highly functionalized lactones **8b**,**c** (Scheme 2). The lactone **8b** was isolated in 92% overall yield from **1b**, and only one diastereomer was obtained. In a similar manner, the lactone **8c** was isolated with excellent diastereo- and enantioselectivity.

One of the major drawbacks in using the *N*-tosyl-α-imino ester **2** for catalytic enantioselective addition reactions has

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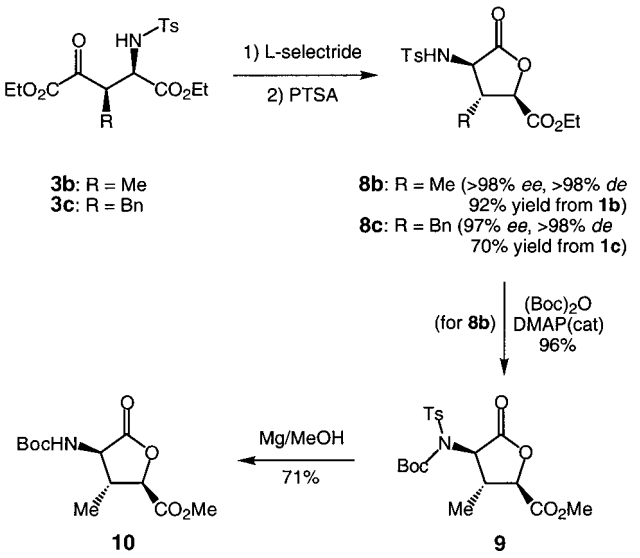
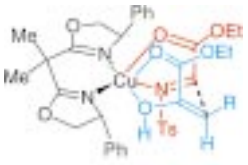


Scheme 2. Formation of lactones **8** from Mannich adducts **3**. The tosyl protecting group was then exchanged for the synthetically more useful Boc group. Boc = *tert*-butoxycarbonyl.

been that the tosyl protecting group is very difficult to remove. We show that we can now remove the tosyl group and exchange it with the much more attractive Boc group,[8] and one example is presented in Scheme 2. Treatment of the lactone **8b** with di-*tert*-butyldicarbonate and DMAP gave the Boc-protected lactone **9** in 98% yield. The reaction of **9** with Mg/MeOH resulted in the selective removal of the *N*-tosyl substituent, and the Boc-protected lactone **10** was isolated in 71% yield.

The lactones **8c** and **9** were isolated as crystalline products and the structures were characterized by X-ray analysis (see Supporting Information). These gave the absolute configuration for the three stereogenic centers in the product as (2*R*,3*R*,4*R*). The absolute configuration allows us to suggest that **11** accounts for both the diastereo- and enantioselectivity of the reaction. The first crucial step is the generation of the enol form (green in **11**) of the carbonyl compound and it is proposed that the copper(II) Lewis acid acts as the catalyst for the formation of the enol.[9] The enol formed can undergo the Mannich reaction after further coordination of the *N*-tosyl-α-imino ester **2** (red in **11**) to the chiral BOX-Cu^{II} catalyst. In the proposed cyclohexane-like transition-state model with a chair conformation, the enol coordinates to the metal in a bidentate fashion, with the R substituent of the enol in the less sterically crowded equatorial position, which is required to obtain the observed diastereoselectivity. We also propose a bidentate coordination of the imine **2**, with the tosyl substituent pointing away from the ligand.



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In conclusion, a new direct catalytic highly enantioselective Mannich reaction of carbonyl compounds with an *N*-tosyl-α-imino ester has been presented. The reaction gives highly functionalized 4-oxo-glutamic acid ester derivatives in high yield and diastereoselectivity, and excellent enantioselectivity which were converted into highly functionalized, optically active α-amino-γ-lactones.

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