Catalytic asymmetric homo-aldol reaction of pyruvate—a chiral Lewis acid catalyst that mimics aldolase enzymes

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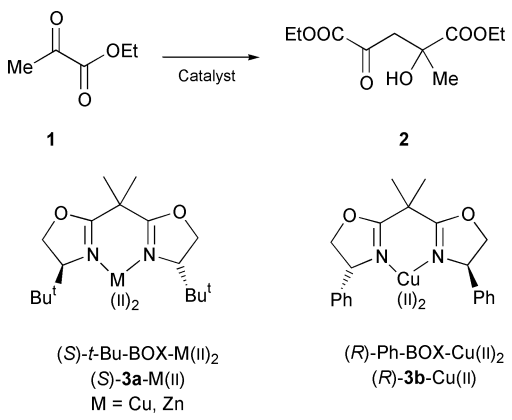
The first catalytic asymmetric homo-aldol reaction of ethyl pyruvate leading to diethyl-2-hydroxy-2-methyl-4-oxoglutarate in up to 96% enantiomeric excess is reported; this reaction has been investigated for various catalysts, amines and solvents, and it is demonstrated that this new reaction leads to a simple synthetic procedure for the formation of optically active isotetronic acid derivatives.

The aldol reaction is one of the most powerful methods for the formation of C–C bonds. The ability to control the absolute configuration of the newly formed stereogenic centre is of fundamental importance. Nature has solved this problem using enzymes and a variety of different aldolase enzymes can catalyse the aldol reaction.[1] For the chemist, the search for methods that predictably transfer chirality catalytically and efficiently by reagent control is a challenging goal. In recent years a number of methods have been developed for the catalytic asymmetric aldol reaction with both high efficiency and enantioselectivity.[2]

In nature aldolase enzymes typically catalyse the stereoselective addition of a ketone donor to a carbonyl acceptor, while the chemical methods normally require more reactive species such as silyl enol ethers,[3] enol-methyl ethers,[4] or ketene silyl acetals,[3a–c,5] except for the multifunctional catalyst systems, containing a Lewis acid and a Brønsted base.[6] This communication presents the first chiral Lewis acid complex acting as a 'pyruvate-dependent aldolase', *i.e.* a type II aldolase, that catalyses a highly enantioselective homo-aldol reaction of ethyl pyruvate.[7] Furthermore, it will be shown that the reaction can be used for the synthesis of an optically active isotetronic acid derivative in two steps, a significant improvement compared with recent multi-step and complex synthetic approaches.[8]

Chiral bisoxazoline–metal(II) complexes are known to act as effective catalysts for enantioselective addition reactions to carbonyl groups.[9] Ethyl pyruvate **1** reacts in the presence of chiral bisoxazoline–metal(II) complexes[3c,d,10] in a homo-aldol reaction to give diethyl-2-hydroxy-2-methyl-4-oxoglutarate **2** [eqn. (1)] and some representative results are shown in Table 1.



(1)

The homo-aldol reaction of ethyl pyruvate **1** proceeds with > 80% conversion. The reaction of **1** catalysed by (*S*)-**3a**-Cu(OTf)$_2$ (10 mol%) gives diethyl-2-hydroxy-2-methyl-4-oxoglutarate **2** with 65% ee (entry 1). The (*S*)-**3a**-Zn(OTf)$_2$ complex can also catalyse the homo-aldol reaction of **1**, but the other enantiomer of **2** is formed with low ee (entry 2). The addition of *N*,*N*-dimethylaniline (DMA) to the reaction increases the ee of **2** and for the reaction catalysed by (*S*)-**3a**-Cu(OTf)$_2$ (10 mol%) and DMA (5 mol%) 96% ee is achieved (entries 3, 4). The enantioselectivity of the homo-aldol reaction is dependent on the amine added. For the other amines tested the highest ee is 93% using PhNBn$_2$ (entry 7), while *e.g.* 60% ee is obtained for Et$_3$N (entry 9).

The enantioselectivity of the homo-aldol reaction of ethyl pyruvate **1** catalysed by (*S*)-**3a**-Cu(II) is dependent on the copper(II) counterion, the solvent and amine as shown in Table 2. For the reaction catalysed by (*S*)-**3a**-Cu(OTf)$_2$ in the presence of 10 mol% DMA in Et$_2$O and THF, 79% ee and 69% ee of the same enantiomer of **2** are obtained, respectively (entries 1, 2). Changing the solvent to CH$_2$Cl$_2$ leads to a change of enantioselection to 12% of the other enantiomer of **2** in the presence of 10 mol% DMA (entry 3). The homo-aldol reaction is also dependent on the counterion. Changing the counterion from OTf to SbF$_6$ in CH$_2$Cl$_2$, in the absence of an amine, leads to a drop in enantioselectivity of **2** from 11% ee to 0% ee (entries 4, 5). This counterion effect in CH$_2$Cl$_2$ is more dramatic in the presence of 10 mol% DMA, as a change in ee from 12% to 63% was observed (entries 3, 7). When using the (*S*)-**3a**-Cu(SbF$_6$)$_2$ catalyst an increase in ee of homo-aldol product **2** by adding 10 mol% DMA occurs in CH$_2$Cl$_2$ (entries 5, 7). To study the effect of different amines on the enantioselectivity of the (*S*)-**3a**-Cu(SbF$_6$)$_2$ catalysed reaction in CH$_2$Cl$_2$, Et(i Pr)$_2$N, PhNBn$_2$ and CyNMe$_2$ were screened. A drop in ee from 63% in the presence of DMA (entry 8) to 30% was found for Et(i Pr)$_2$N (entry 11), but we were pleased to observe an increase in ee to 75% and 77% for PhNBn$_2$ and CyNMe$_2$, respectively (entries 9, 10).

It is important to note that the enantioinduction of the (*S*)-**3a**-Cu(II) catalytic system can be switched by changing only one

Table 1 Homo-aldol reaction of ethyl pyruvate **1** in the presence of (*S*)-**3a**-M(OTf)$_2$ (M = Cu, Zn) and (*R*)-**3b**-Cu(OTf)$_2$ and various amines in Et$_2$O at room temperature[a]

Entry	Catalyst/ (mol%)[b]	Amine (mol%)[b]	Ee[c,d] (%)
1	(*S*)-**3a**-Cu(OTf)$_2$ (10)	—	(−)-65
2	(*S*)-**3a**-Zn(OTf)$_2$ (10)	—	(+)-7
3	(*S*)-**3a**-Cu(OTf)$_2$ (10)	DMA[e] (10)	(−)-79
4	(*S*)-**3a**-Cu(OTf)$_2$ (10)	DMA[e] (5)	(−)-96
5	(*S*)-**3a**-Zn(OTf)$_2$ (10)	DMA[e] (10)	(+)-16
6	(*R*)-**3b**-Cu(OTf)$_2$ (10)	DMA[e] (10)	(+)-28
7	(*S*)-**3a**-Cu(OTf)$_2$ (10)	PhNBn$_2$ (10)	(−)-93
8	(*S*)-**3a**-Cu(OTf)$_2$ (10)	CyNMe$_2$[f] (10)	(−)-50
9	(*S*)-**3a**-Cu(OTf)$_2$ (10)	Et$_3$N (10)	(−)-60
10	(*S*)-**3a**-Cu(OTf)$_2$ (10)	Et(i Pr)$_2$N (10)	(−)-67

[a] All reactions give > 80% conversion, except for entry 2 which gives 40% conversion. [b] Relative to ethyl pyruvate. [c] Ee measured by GC using a Chrompack CP-Chirasil Dex CB (β-PM) column. [d] (+)/(−), sign of the optical rotation of isotetronic acid derivative (**4**). [e] DMA = *N*,*N*-dimethylaniline. [f] Cy = cyclohexyl.

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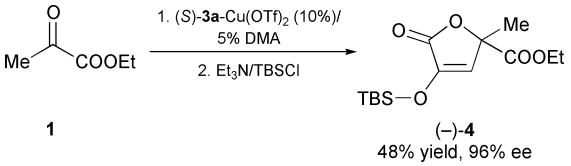
Table 2 Homo-aldol reaction of ethyl pyruvate **1** catalysed by (*S*)-**3a**-Cu(II) in the presence of OTf and SbF_6 as counterions and various amines in different solvents[a]

Entry	Catalyst (mol%)[b]	Amine (mol%)[b]	Solvent	Ee[c,d] (%)
1	(*S*)-**3a**-Cu(OTf)$_2$ (10)	DMA[e] (10)	Et_2O	(−)-79
2	(*S*)-**3a**-Cu(OTf)$_2$ (10)	DMA[e] (10)	THF	(−)-69
3	(*S*)-**3a**-Cu(OTf)$_2$ (10)	DMA[e] (10)	CH_2Cl_2	(+)-12
4	(*S*)-**3a**-Cu(OTf)$_2$ (10)	—	CH_2Cl_2	(−)-11
5	(*S*)-**3a**-Cu(SbF_6)$_2$ (10)	—	CH_2Cl_2	0
6	(*S*)-**3a**-Cu(SbF_6)$_2$ (10)	—	Et_2O	(−)-50
7	(*S*)-**3a**-Cu(SbF_6)$_2$ (10)	DMA[e] (10)	CH_2Cl_2	(+)-63
8	(*S*)-**3a**-Cu(SbF_6)$_2$ (10)	DMA[e] (10)	Et_2O	(+)-24
9	(*S*)-**3a**-Cu(SbF_6)$_2$ (10)	$PhNBn_2$ (10)	CH_2Cl_2	(+)-75
10	(*S*)-**3a**-Cu(SbF_6)$_2$ (10)	$CyNMe_2$[f] (10)	CH_2Cl_2	(+)-77
11	(*S*)-**3a**-Cu(SbF_6)$_2$ (10)	Et(^{i}Pr)$_2$N (10)	CH_2Cl_2	(+)-30

[a] All reactions give 70–80% conversion, except entry 11 (25% conversion). [b] Relative to ethyl pyruvate. [c] Ee measured by GC using Chrompack CP-Chirasil Dex CB (β-PM) column. [d] (+)/(−), sign of the optical rotation of isotetronic acid derivative (**4**). [e] DMA = *N*,*N*-dimethylaniline. [f] Cy = cyclohexyl.

parameter: the solvent (entry 1 *vs*. 3; Et_2O *vs*. CH_2Cl_2), the counterion (entry 1 *vs*. 8; OTf *vs*. SbF_6) or the presence of an amine (entry 6 *vs*. 8; no amine *vs*. 10 mol% DMA). At the present stage of investigations we are not able to fully account for the change in reaction course, but work is ongoing to elucidate the reaction mechanism.

The chiral bisoxazoline–metal(II) complex, (*S*)-**3a**-Cu(II) (M = OTf, SbF_6), is thus a simple chiral Lewis acid complex which mimics the pyruvate-dependent type II aldolase. This new catalytic enantioselective reaction can be used for the synthesis of the optically active isotetronic acid derivative **4** [eqn. (2)].



1 (−)-**4** 48% yield, 96% ee (2)

Isotetronic acids have been found to exhibit important biological effects such as aldose reductase inhibitory activity[11] and antitumor activity.[12] Reaction of the homo-aldol product **2** with Et_3N and TBSCl gives **4** in 48% isolated yield (from **1**)† under non-optimised reaction conditions.[13] The formation of **4** where the catalytic enantioselective approach is the first step, is a significant improvement compared to the multi-step and complex synthetic approaches previously reported.[8]

In summary, a catalytic highly enantioselective homo-aldol reaction of ethyl pyruvate giving diethyl-2-hydroxy-2-methyl-4-oxoglutarate in up to 96% ee has been developed. This reaction which mimics the pyruvate-dependent aldolase can be used for the preparation of optically active isotetronic acid derivatives in two steps.

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Notes and references

† Representative procedure for the catalytic asymmetric homo-aldol reaction: To an oven or flame dried Schlenk flask Cu(OTf)$_2$ (36.2 mg, 0.10 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (32.4 mg, 0.11 mmol) were added. The mixture was stirred under vacuum for 2 h and filled with Ar. Dry solvent (2 mL) was added and the solution was stirred for 2 h. The amine was added followed by the addition of ethyl pyruvate (110 μL, 1.0 mmol). The reaction mixture was stirred for 40 h and was then flushed through a plug of silica with Et_2O as the eluent. Solvent was removed *in vacuo* and the residue was redissolved in CH_2Cl_2 followed by the addition of dry Et_3N (200 μL, 1.5 mmol) and TBSCl (196 mg, 1.3 mmol). The solution was stirred overnight and was purified by FC (SiO_2, 12% Et_2O–pentane) to yield 3-*tert*-butyldimethylsilyloxy-5-methyl-2-oxo-2,5-dihydrofuran-5-carboxylic acid ethyl ester (**4**) as a clear colourless oil (72 mg, 0.24 mmol, 48%).^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.23 (s, 1H), 4.21 (q, J = 7.2, 2H), 1.69 (s, 3H), 1.27 (t, J = 7.2, 3H), 0.96 (s, 9H), 0.24 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.0, 168.1, 143.2, 124.4, 81.7, 62.4, 25.4, 22.9, 18.3, 14.0, 1.0; IR : ν/cm^{-1}: 2958 (m), 2934 (m), 2861 (m), 1890 (s), 1745 (s), 1656 (s), 1473 (w), 1330 (w), 1257 (s), 1208 (s), 1097 (s); HRMS: calcd. for $C_{14}H_{24}O_5Si$ [M + Na]$^+$ 323.1291, found 323.1290; $[\alpha]_D^{23}$ = −84 (c = 0.01, CH_2Cl_2) 96% ee by chiral GC using a Chrompack CP-Chirasil Dex CB (β-PM) column, τ(major) = 20.3 min, τ(minor) = 20.6 min.

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