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Direct catalytic asymmetric aldol reactions of pyruvates: scope and mechanism

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The direct aldol reaction of 2-ketoesters catalyzed by chiral bisoxazoline copper(II) complexes has been investigated. First the direct homo-aldol reaction of ethyl pyruvate is reported which proceeds to give diethyl 2-hydroxy-2-methyl-4-oxoglutarate. This was isolated as the more stable optically active isotetronic acid in good yield and enantiomeric excess in the absence of bases such as amines. Detailed investigations of the use of different chiral Lewis acids as the catalyst, amines, ratios of chiral bisoxazoline copper(II) salts : amine, and solvents gave up to 96% ee of the isotetronic acid. Then the reaction was extended to a cross-aldol reaction of various 2-ketoesters with activated carbonyl compounds to give the cross-aldol adduct with excellent enantiomeric excess. Furthermore, the synthesis of the isotetronic acids was investigated from these cross-aldol adducts giving important information about the formation of the stereogenic centers during the aldol reaction. Based on the absolute configuration of the homo-aldol adduct the mechanism for the aldol reaction is discussed.

Introduction

The formation of C–C bonds by the aldol reaction is a powerful reaction in organic chemistry and especially the ability to control the stereochemistry of the newly formed stereogenic center(s) is of fundamental importance.

The stereochemistry of the chiral carbon atom(s) created by the aldol reaction can be controlled in different ways. In nature aldol reactions are catalyzed by various aldolase enzymes and the adducts are formed with excellent enantioselectivity.[1] For the chemist, the search for synthetic procedures that predictably transfer chirality catalytically and efficiently is a challenging goal. Therefore, the development of catalytic asymmetric aldol reactions has been a challenge to chemists.[2] In recent years a number of synthetic procedures have been developed for catalytic asymmetric aldol reactions with both high efficiency and enantioselectivity.[2]

One of the great challenges for the aldol reaction is the generation of the nucleophile – the donor. Nature has solved this challenge by the aldolase enzymes which typically catalyze the stereoselective addition of a ketone donor to a carbonyl acceptor. However, until recently the chemical methods[2,3] have normally required more reactive species such as silyl-enol ethers,[4] enol-methyl ethers,[5] or ketene-silyl acetals.[4a–c,6]

A way to improve the efficiency of the chemical methods for the aldol reaction is the development of a catalytic system where the prior stoichiometric formation of *e.g.* the silyl enolate is not necessary, *i.e.* to perform direct aldol reactions similar to the aldolase enzymes. Shibasaki *et al*. have developed a new family of heterobimetallic catalysts, containing a Lewis acid and a Brønsted base, which can catalyze the direct addition of enolisable ketones to aldehydes with up to 95% ee.[7] Trost *et al.* have also developed a bimetallic catalyst for the direct asymmetric aldol reaction.[8] This catalyst consists of a ligand derived from L-proline with two equivalents of Et_2Zn added to the ligand and has been applied to similar reactions to those studied by Shibasaki *et al*. For this chiral zinc catalyst, only 2.5–5 mol% was necessary to obtain very high enantioselectivities. The direct catalytic asymmetric aldol reaction can also be achieved using organocatalysis and several examples using *e.g.* L-proline as catalyst have appeared.[9] These reactions proceed for simple carbonyl compounds with high enantioselectivities.

In this paper we report that chiral Lewis acid complexes can act as a pyruvate-dependent aldolase, *i.e.* a type II aldolase, to catalyze the direct enantioselective aldol reaction of 2-ketoesters, such as ethyl pyruvate (eqn. 1).[10,11] The products obtained from this direct catalytic enantioselective aldol reaction can be applied for the synthesis of optically active isotetronic acid derivatives in two steps. The synthesis of these isotetronic acids is an improvement compared to recent published procedures, which require multi-step reactions and complex synthetic approaches.[12]

(1)

The homo-aldol reaction of 2-ketoesters such as ethyl pyruvate has been reported before. A photoinduced cobalt(III) catalyzed homo-aldol reaction of ethyl pyruvate was reported by Kijima *et al.*[13] In this reaction, ethyl pyruvate was irradiated by a tungsten lamp in the presence of a catalytic amount (0.2 mol%) of benzyl(pyridine)cobaloxime affording 42% yield of homo-aldol product *via* a proposed radical mechanism. The reaction did not proceed without both irradiation and the cobaloxime. The homo-aldol products have also been found as side products in reactions where strong bases have been applied, *e.g.* in Grignard reactions[14] or in the formation of silyl enol ethers of 2-ketoesters using potassium hydride.[15]

Results and discussion

The catalytic enantioselective homo-aldol reaction of ethyl pyruvate **1a** was discovered during our investigations of catalytic asymmetric Friedel–Crafts reactions.[16] In this reaction, electron-rich aromatic compounds, such as *N*,*N*-di-

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Table 1 [a] Screening of different amines in the (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$-catalyzed homo-aldol reaction of ethyl pyruvate **1a** in Et$_2$O

Entry	Amine (10 mol%)	**4a** ee[b] (%)
1	—	(*S*)-65
2	DMA	(*S*)-79
3	DBA	(*S*)-93
4	$CyNMe_2$	(*S*)-50
5	Et_3N	(*S*)-60
6	Et(*i*-Pr)$_2$N	(*S*)-67
7	Imidazole	(*S*)-58

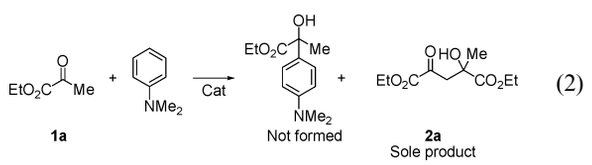
[a] All reactions gave > 80% conversion. [b] Measured by chiral GC.

Table 2 [a] Amine screening in the (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$-catalyzed homo-aldol reaction of ethyl pyruvate **1a** in Et$_2$O

Entry	Amount (mol%)	DMA **4a** ee[b] (%)	DBA **4a** ee[b] (%)
1	1	(*S*)-88	(*S*)-82
2	2.5	(*S*)-94	(*S*)-78
3	5	(*S*)-96	(*S*)-77
4	7.5	(*S*)-87	(*S*)-57
5	10	(*S*)-79	(*S*)-93
6	20	(*S*)-69	(*S*)-39

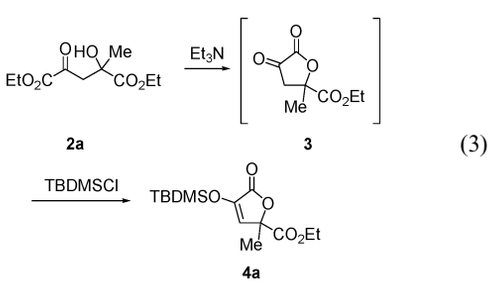
[a] All reactions gave > 80% conversion. [b] Measured by chiral GC.

methylaniline (DMA), reacted with ethyl glyoxylate, or the highly activated ethyl trifluoropyruvate, in the presence of chiral bisoxazoline–Cu(OTf)$_2$ as the catalyst giving mandelic acid derivatives with up to 94% ee. In an attempt to broaden the scope of this reaction, DMA was reacted with ethyl pyruvate **1a** (eqn. 2). However, formation of the expected mandelic acid ester derivative was not observed. Instead, > 80% conversion of **1a** to the homo-aldol adduct, diethyl 2-hydroxy-2-methyl-4-oxoglutarate **2a**, was observed in the ^{1}H NMR spectrum of the crude product.[11]



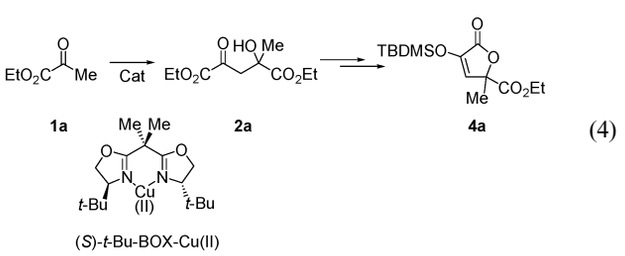
(2)

Unfortunately, the homo-aldol adduct **2a** was found to be unstable when trying to isolate it by flash chromatography. Therefore, it was necessary to develop a reaction protocol that would ensure smooth conversion of **2a** into a stable isolable compound. Treatment of **2a** with a base such as Et_3N led to lactone **3**.[11] However, this compound was also unstable,[17] but could be protected as the *tert*-butyldimethylsilyl enol ether **4a**, which is the attractive isotetronic acid derivative (eqn. 3).[12]



(3)

A series of different chiral Lewis acids has been tested as catalysts for the direct homo-aldol reaction of ethyl pyruvate **1a** and among the catalysts tested, the *tert*-butyl-bisoxazoline[18–34] copper(II) complex gave the most promising results. To find the optimal reaction conditions for the homo-aldol reaction of **1a** several different amines were tested as additives in the reaction catalyzed by (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ (10 mol%) in Et$_2$O at room temperature (eqn. 4). After 40 h, the reaction mixture was flushed through a plug of silica to remove the catalyst and the conversion was determined by ^{1}H NMR-spectroscopy. The



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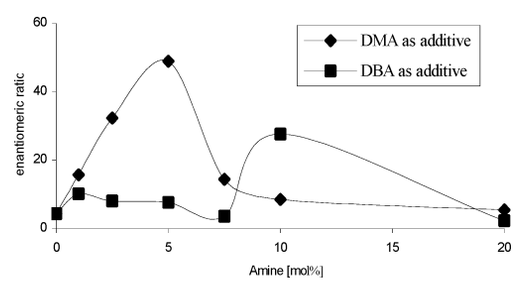


Fig. 1 Enantiomeric ratio of **4a** *vs.* amine loadings.

The graph in Fig. 1 depicting the effect of the concentration of DMA relative to ethyl pyruvate **1a** on the enantiomeric ratio of the homo-aldol product **4a** has a maximum at 5 mol%. That is, 50 mol% of DMA relative to the catalyst loading. The same trend was observed with lower catalyst loading; 5 mol% (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ and 2.5 mol% DMA gave 88% ee, while 5 mol% (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ and 10 mol% DMA gave only 53% ee. In a less 'well-behaved' curve an optimal concentration of DBA is found to be 10 mol% relative to **1a**. It should be noted that the optimal conditions for both amines were applied three times for DMA and twice for DBA with consistent results. A more detailed discussion of these results is provided later in the paper, however, Fig. 1 shows that high amine concentrations lead to a crowded dominant copper complex which confers poor enantioinduction on the homo-aldol product.

The solvent effect on the homo-aldol reaction of ethyl pyruvate **1a** was also examined. With 5 mol% (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ and 2.5 mol% DMA the solvent was varied. The

Table 3 Solvent screening for the homo-aldol reaction of ethyl pyruvate **1a** catalyzed by 5 mol% (*S*)-*t*-Bu-BOX–$Cu(OTf)_2$ and 2.5 mol% DMA

Entry	Solvent	**4a** ee[a] (%)
1	Et_2O	(*S*)-88
2	THF	(*S*)-59
3	PhMe	(*S*)-62
4	PhH	(*S*)-55
5	CH_2Cl_2	(*R*)-21

[a] Measured by chiral GC.

Table 4 [a] Homo-aldol reaction of ethyl pyruvate **1a** in the presence of (*S*)-*t*-Bu-BOX–$Cu(SbF_6)_2$ (10 mol%) as the catalyst and 10 mol% amine

Entry	Solvent	Amine	**4a** ee[b] (%)
1	Et_2O	—	(*S*)-50
2	Et_2O	DMA	(*R*)-24
3	CH_2Cl_2	—	0
4	CH_2Cl_2	DMA	(*R*)-63
5	CH_2Cl_2	$Et(i\text{-}Pr)_2N$	(*R*)-30
6	CH_2Cl_2	$CyNMe_2$	(*R*)-77
7	CH_2Cl_2	DBA	(*R*)-75

[a] All reactions gave 70–80% conversion, except entry 5 (25% conversion). [b] Measured by chiral GC.

conversions of **1a** were high in all solvents (70–88%) and the enantioselectivities of **4a** are shown in Table 3.

Changing the solvent from Et_2O to THF, toluene or benzene did not improve the enantioselectivity of the reaction (Table 3, entries 1–4), but interestingly the enantioselectivity was reversed when the reaction was performed in CH_2Cl_2 (entry 5) although the same enantiomer of the bisoxazoline ligand was applied. It should be noted that solvent dependent enantioselectivity has been observed before for reactions catalyzed by copper-bisoxazolines, however, in our previous investigations this was found for hetero-Diels–Alder reactions catalyzed by chiral phenyl-bisoxazoline-copper(II) complexes.[35,36] The reactions in CH_2Cl_2 were very water-sensitive. If non-dried CH_2Cl_2 was used, the (*S*)-enantiomer was in excess ((*S*)-11% ee) and in one example (*R*)-61% ee was obtained in dry CH_2Cl_2. Unfortunately the latter result could not be reproduced, with further runs in dry CH_2Cl_2 yielding product with (*R*)-21% ee.

The reactions described above were all catalyzed by (*S*)-*t*-Bu-BOX–$Cu(OTf)_2$. It was found that subtle changes in reaction conditions had a large effect on the enantioselectivities of the homo-aldol reaction of ethyl pyruvate **1a**. Therefore, we decided to investigate the effect of changing the anion of the copper salt to the less coordinating hexafluoroantimonate ion, (SbF_6^-). The screening-results for the (*S*)-*t*-Bu-BOX–$Cu(SbF_6)_2$-catalyzed homo-aldol reaction (eqn. 4) under various reaction conditions are shown in Table 4.

Changing the counterion of the (*S*)-*t*-Bu-BOX–Cu(II) catalyst certainly had an effect on the enantioselectivity of the homo-aldol reaction of ethyl pyruvate **1a**. In Et_2O as the solvent however, the result using $Cu(SbF_6)_2$ as the Lewis acid was similar to the $Cu(OTf)_2$-catalyzed reaction when an amine was not added to the reaction (Table 1, entry 1, *vs.* Table 4, entry 1). In the presence of 10 mol% DMA the enantioselectivity was reversed and 24% ee of the opposite enantiomer was obtained (Table 4, entry 2) compared to the $Cu(OTf)_2$-catalyzed reaction. In CH_2Cl_2, the results were capricious without the presence of an amine. This inconsistency was eliminated by the presence of 10 mol% of an amine during the reaction, and depending on the amine, up to 77% ee of the (*R*)-enantiomer of **2a** could be regularly obtained (entries 4–7).

The promising results with DMA, DBA and $CyNMe_2$ as additives in CH_2Cl_2 for the catalytic enantioselective homo-aldol reaction catalyzed by (*S*)-*t*-Bu-BOX–$Cu(SbF_6)_2$ led us to investigate the properties of various chlorinated solvents in the reaction. The results are shown in Table 5 and the enantiomeric ratios are plotted as a function of the dielectric constants of the solvents in Fig. 2.

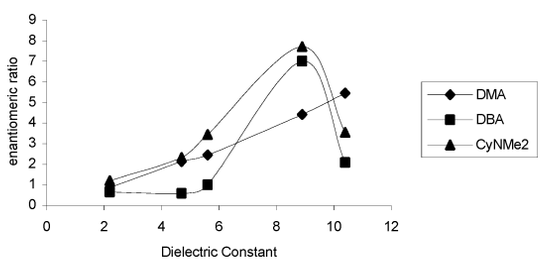


Fig. 2 Enantiomeric ratio *vs.* dielectric constant.

The general trend of the results depicted in Fig. 2 is that higher enantioselectivities of (*R*)-**2a** are obtained in more polar chlorinated solvents. This could indicate that – relative to the transition state leading to the (*S*)-enantiomer – the transition state leading to the (*R*)-enantiomer is to some extent stabilized by non-coordinating polar solvents. The best enantioselectivities in a chlorinated solvent using 10 mol% of (*S*)-*t*-Bu-BOX–$Cu(SbF_6)_2$ were in CH_2Cl_2 using either 10 mol% DBA or $CyNMe_2$.

The catalytic properties of chiral zinc(II) complexes were also examined in the homo-aldol reaction of ethyl pyruvate **1a**. The use of 10 mol% $Zn(OTf)_2$ in combination with the *tert*-butyl-bisoxazoline ligand gave only low conversion of **1a** in Et_2O and CH_2Cl_2. In the presence of 10 mol% DMA the conversion was slightly higher, however, only up to 16% ee of **2a** was obtained.

In order to develop the direct catalytic enantioselective aldol reaction further to encompass cross-aldol reactions, considerations regarding the reactivity have to be taken into account. The function of ethyl pyruvate **1a** is to act as the donor in the reaction, and then the acceptor has to be more electrophilic than **1a**. Ethyl trifluoropyruvate **5** is a non-enolisable ketone and more electrophilic than ethyl pyruvate due to the electron-withdrawing trifluoromethyl group. Furthermore, it has the 2-ketoester functionality allowing chelation to the copper(II) catalyst. To our delight the (*S*)-*t*-Bu-BOX–$Cu(OTf)_2$-catalyzed cross-aldol reaction of **1a** with ethyl trifluoropyruvate **5**

Table 5 [a] Catalytic enantioselective homo-aldol reaction of ethyl pyruvate **1a** catalyzed by (*S*)-*t*-Bu-BOX–$Cu(SbF_6)_2$ (10 mol%) and 10 mol% amine in different chlorinated solvents

Entry	Solvent	Dielectric constant (ε)	DMA ee[b] (%)	DBA ee[b] (%)	$CyNMe_2$ ee[b] (%)
1	CCl_4	2.2	(*S*)-7	(*S*)-21	(*R*)-9
2	$CHCl_3$	4.7	(*R*)-36	(*S*)-25	(*R*)-40
3	PhCl	5.6	(*R*)-42	0	(*R*)-55
4	CH_2Cl_2	8.9	(*R*)-63	(*R*)-75	(*R*)-77
5	$ClCH_2CH_2Cl$	10.4	(*R*)-69	(*R*)-35	(*R*)-56

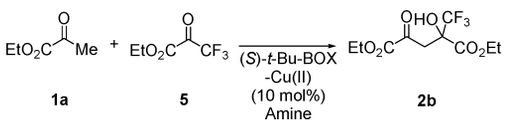
[a] All reactions gave 70–80% conversion. [b] Measured by chiral GC.

Table 6 Catalytic enantioselective cross-aldol reaction of ethyl pyruvate **1a** with ethyl trifluoropyruvate **5** catalyzed by (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ (10 mol%) in the presence of amines using Et_2O as the solvent

Entry	Amine (mol%)	Temp. (°C)	Conv.[a] (%)	**2b** ee[b] (%)
1	—	rt[c]	> 80	42
2	—	0	50	49
3	—	−15	40	47
4	DMT (5)	rt[c]	> 80	18
5	DMT (10)	rt[c]	> 90	12
6	DMT (5)	−15	40	39
7	DMT (10)	−15	40	31
8	DBT (5)	−15	40	39
9	DBT (10)	−15	40	39
10	$CyNMe_2$ (5)	−15	40	42

[a] Determined by ^{1}H NMR spectroscopy. [b] Measured by chiral GC. [c] rt = room temperature.

proceeded to give diethyl 2-hydroxy-2-trifluoromethyl-4-oxoglutarate **2b** (eqn. 5).



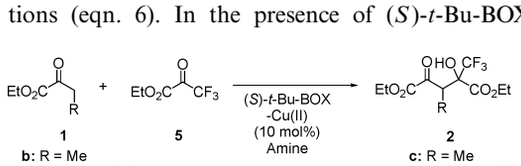
1a 5 2b (5)

The present reaction gives an easy approach to chiral compounds containing the trifluoromethyl group which have found application in various fields.[37] Some results of this reaction with Et_2O as solvent are presented in Table 6.

The cross-aldol reaction of ethyl pyruvate **1a** with ethyl trifluoropyruvate **5** proceeded with high conversion at room temperature and gave **2b** with moderate enantioselectivity without the presence of an amine (Table 6, entry 1). Lowering of the reaction temperature gave only a marginal increase in enantioselectivity but a significant drop in conversion (entries 2,3). The addition of amines had a positive effect on the enantioselectivity of the homo-aldol reaction of **1a** (see Table 1). However, DMA and DBA would be unsuitable additives in the cross-aldol reaction as these aromatic amines undergo copper(II)-catalyzed Friedel–Crafts alkylation with ethyl trifluoropyruvate.[16] A methyl substituent in the *para*-position of these aromatic amines would only have a small effect on the electronic and steric properties of the amines, but would prevent the Friedel–Crafts alkylation reaction. Therefore, *N*,*N*-dimethyl-*p*-toluidine (DMT) and *N*,*N*-dibenzyl-*p*-toluidine (DBT) were added instead of DMA and DBA. Surprisingly, the addition of DMT lowered the enantioselectivity of the reaction (entries 4,5); at –15 °C the presence of DMT had a less pronounced effect, and slightly lower enantioselectivities were measured (entries 6,7). The same trend was observed when DBT or $CyNMe_2$ was added to the reaction (entries 8–10).

We have also applied (*S*)-*t*-Bu-BOX–Cu(SbF$_6$)$_2$ (10 mol%) in CH_2Cl_2 as catalyst for direct cross-aldol reactions (eqn. 5). This catalyst gave the opposite enantiomer of **2b** in agreement with the results obtained in the homo-aldol reaction of ethyl pyruvate. Unfortunately, the enantioselectivities were very low (< 20% ee).

The higher electrophilicity of ethyl trifluoropyruvate **5** led us to investigate 2-ketoesters with substituents in the 3-position such as ethyl 2-ketobutyrate **1b** under various reaction conditions (eqn. 6). In the presence of (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$



1 5 2 (6)

b: R = Me
c: R = CH_2-*c*-C_6H_{11}
d: R = $CH_2CH_2CH{=}CH_2$
e: R = *n*-C_5H_{11}
f: R = *i*-Bu

c: R = Me
d: R = CH_2-*c*-C_6H_{11}
e: R = $CH_2CH_2CH{=}CH_2$
f: R = *n*-C_5H_{11}
g: R = *i*-Bu

Table 7 [a] Catalytic enantioselective cross-aldol reaction of ethyl 2-ketobutyrate **1b** with ethyl trifluoropyruvate **5** catalyzed by (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ in the presence of amines in Et_2O as the solvent

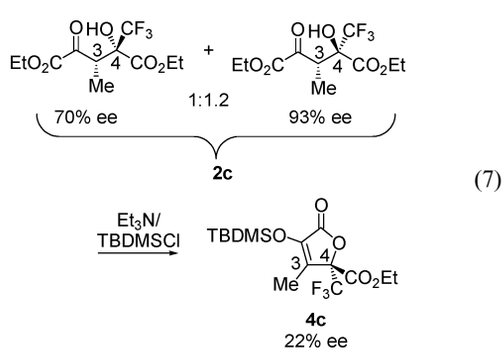
Entry	Amine (mol%)	Temp. (°C)	dr	ee[b] (%)
1	—	rt[c]	1.0 : 1.2	70/93
2	DMT (5)	−15	1.8 : 1.0	89/92
3	DMT (10)	−15	1.4 : 1.0	92/95
4	DBT (5)	−15	1.0 : 1.3	69/93
5	$CyNMe_2$ (5)	−15	1.1 : 1.0	81/93

[a] All reactions > 80% conversion. [b] Measured by chiral GC. [c] rt = room temperature.

(10 mol%), the cross-aldol reaction of **1b** with **5** proceeded well in Et_2O with good conversions in most cases (up to full conversion) (eqn. 6). Some representative results are shown in Table 7.

It appears from the results in Table 7 that the enantioselectivity of the cross-aldol adduct **2c** is very high as up to 95% ee is obtained (entry 3). However, the diastereoselectivity was low, and interestingly, the additives only seemed to have an influence on the enantioselectivities of one of the diastereomers, while the enantioselectivities were consistently high of the other. This observation suggests that at least two different transition states are operating in the cross-aldol reaction. The additive only has an influence on one of these transition states.

If the mixture of the diastereomers of **2c** from Table 7, entry 1 is subjected to the same reaction conditions as the homo-aldol product **2a** (eqn. 3), the isotetronic acid derivative **4c** is obtained with an enantiomeric excess of 22% ee (eqn. 7). It should be noted that the relative and absolute configurations in eqn. 7 are chosen arbitrarily, but are shown to illustrate the reason for the low enantioselectivity of **4c**.



(7)

If one assumes the two diastereomers of **2c** have the relative and absolute configurations as shown in eqn. 7 then the ratio between the four stereoisomers is (3*S*,4*S*) : (3*R*,4*R*) : (3*R*,4*S*) : (3*S*,4*R*) = 0.39 : 0.07 : 0.02 : 0.52 calculated from the enantiomeric excesses of the two diastereomers and the diastereomeric ratio. In the isotetronic acid derivative **4c**, C-3 is no longer a chiral center, while C-4 still is, with 22% ee measured by chiral GC and 19% ee calculated from the diastereomeric ratio and the enantiomeric excesses of the two diastereomers. This supports the hypothesis that the major enantiomers of the two diastereomers have the same absolute configuration at C-3. Similar results are obtained for the formation of the isotetronic acid **4g**.

The cross-aldol reaction was studied for the reaction of the ethyl 2-ketoesters **1b**–**f** in the presence of (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ (10 mol%) in the presence of DMT as the amine in Et_2O as the solvent at room temperature (eqn. 6) and Table 8 shows the results.

It appears from the results in Table 8 that the catalytic enantioselective cross-aldol reaction proceeds in moderate yields for the different 2-ketoesters (**1b**–**f**) studied. We have not tried to optimize reaction conditions for each reaction, but rather have shown that the general reaction conditions developed can be used for the formation of the cross-aldol adducts with excellent

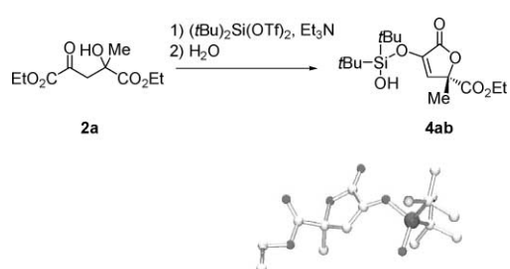
Table 8 Catalytic enantioselective cross-aldol reaction of various ethyl 2-ketoesters **1b–f** with ethyl trifluoropyruvate **5** catalyzed by (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ (10 mol%) in the presence of DMT (5 mol%) in Et$_2$O as the solvent at room temperature

Entry	2-Ketoester	Reaction time (h)	Yield[a] (%)	dr	ee[b] (%)
1[c]	**1b**	48	**4c** - 40	1 : 1.8	89/92
2	**1c**	72	**4d** - 32	1 : 1.2	68/84
3	**1d**	94	**4e** - 50	1 : 1.2	65/96
4[d]	**1d**	144	**4e** - 52	1 : 1.4	85/96
5	**1e**	110	**4f** - 28	1 : 1.2	92/91
6	**1f**	74	**4g** - 66[e]	1 : 1.2	62/75

[a] Isolated yield of corresponding isotetronic acid derivative. [b] Measured by chiral GC of the cross-aldol product. [c] The reaction was performed at −15 °C. [d] The reaction was performed at −24 °C. [e] The formation of the isotetronic derivative from the cross-aldol adduct was performed at 40 °C.

enantioselectivity of the major diastereoisomer formed. It should be noted that the catalytic enantioselective cross-aldol reaction proceeds with full conversion and the reason for the moderate yields in Table 8 is the result of the formation of the isotetronic acid derivative from the cross-aldol adduct. In terms of enantiomeric excess the lowest obtained is for the *i*-butyl derivative **1f** which gives 75% ee of the major diastereomer (Table 8, entry 6), while up to 96% ee is obtained for ethyl 2-keto-6-heptenoate **1d**. Furthermore, it should also be noted that the enantiomeric excess can be improved slightly by lowering the reaction temperature to −24 °C, however, longer reaction times are required; *e.g.* the enantiomeric excess of the minor diastereomer of **4e** is improved from 65% ee at room temperature to 85% ee at −24 °C.

The absolute configuration of the homo-aldol adduct **2a**, formed using the (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ catalyst, has been determined on the basis of transformation of **2a** into the isotetronic ester **4ab** having a silyl-protecting group which allows the formation of crystals suitable for X-ray analysis (Scheme 1). The absolute configuration of the chiral carbon atom in **4ab** was assigned to be (*S*), *i.e.* the (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ catalyst induces the (*S*)-configuration in the homo-aldol adduct. Changing the counterion of the Lewis acid to SbF_6 and maintaining the same enantiomer of the ligand induces the (*R*)-configuration in the reaction with added amines under the same reaction conditions.



Scheme 1 Reaction of homo-aldol adduct **2a** leading to crystalline isotetronic acid derivative **4ab** and the X-ray structure of **4ab**.

The inversion of stereochemistry by changing the counterion, solvent or amine was an unexpected result which we examined judiciously. There have been a few examples in the literature showing this inversion of stereochemistry by only changing reaction conditions.[35,38] The results published herein show one of the greatest changes in enantiomeric excess for a metal-catalyzed asymmetric reaction.

The catalytic enantioselective aldol reactions of 2-ketoesters with the activated carbonyl compounds presented seem to follow a complex reaction path as many factors have influence on the stereochemical outcome of the reaction. The enantiomeric excess can change from (*S*)-96% ee to (*R*)-77% ee by changing the solvent and counterion. Our hypothesis is that there are at least two dominant reaction paths and that the transition state is very sensitive to the reaction conditions, and the inversion of the enantioinduction conferred by the catalyst must be due to dramatic crucial differences in the transition state.

The postulated intermediates are shown in Fig. 3. The (*S*)-**2a** absolute stereochemistry (Fig. 3, left) formed by the (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ catalyzed homo-aldol reaction of ethyl pyruvate is in agreement with previous examples for enantioselective reactions catalyzed by this catalyst.[4c,d,36] These examples involve nucleophilic attack on a bidentately coordinated substrate on copper(II). It should be noted that the angle of the plane of the coordinated 2-ketoester and the plane of the copper-bisoxazoline ligand is *ca.* 45°.[36]

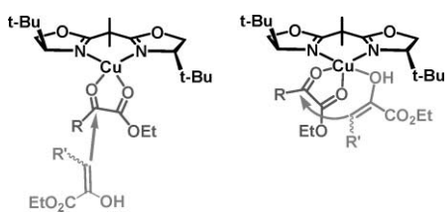


Fig. 3 Proposed intermediates and approaches for the enolate to the bidentate coordinated 2-ketoester.

For the homo-aldol reaction catalyzed by (*S*)-*t*-Bu-BOX–Cu(SbF$_6$)$_2$ we propose that ethyl pyruvate coordinates to the metal center in a bidentate fashion. This allows the copper(II) bound enol-form of ethyl pyruvate to attack the (*Re*)-face of the bidentate coodinated 2-ketoester as shown to the right in Fig. 3. This explanation is consistent with the formation of the (*R*)-enantiomer of **2a** when using (*S*)-*t*-Bu-BOX–Cu(SbF$_6$)$_2$ (see Table 4, entries 2, 4–7). Recently, we reported that for the Henry reaction of nitromethane with 2-ketoesters catalyzed by (*S*)-*t*-Bu-BOX–Cu(OTf)$_2$ the reaction took place *via* a pentacoordinated copper(II) complex.[34a,b] The suggested coordination of nitromethane to the metal center gave rise to an attack of the nitronate form of nitromethane at the (*Re*)-face of the 2-ketoester. Pentacoordinate BOX–Cu(II) complexes have also been proposed as possible transition structures for the Henry reaction between aldehydes and nitromethane by Evans *et al.*[34c]

We postulate that both of the possible intermediates in Fig. 3 are present under the reaction conditions and it is the relative effective turnover which determines the stereochemistry of the product and its enantiomeric excess. To support our hypothesis we must analyze the effects of solvent, counterion and additives on the complexes and keto–enol equilibrium of ethyl pyruvate.

The copper(II) seems to have important properties: (*i*) it might initiate/catalyze the keto to enol tautomerisation by coordination of the keto-functionality and (*ii*) it might coordinate the enol-OH of ethyl pyruvate strongly leading to a stabilization of the enol-form intermediate. Ethyl pyruvate does not undergo the homo-aldol reaction on standing and no homo-aldol product was detected on stirring with the amine bases. The copper(II) center is crucial for formation of the enol-form and reaction to the homo-aldol product, independent of the presence of amine (see Table 1).

This also suggests that an intermediate must be present where the enol-form of ethyl pyruvate is bound to the copper(II) center. The key question is whether the enol remains co-

ordinated in the reactive intermediate, or if the enol is required to uncoordinate from the copper(II), and subsequently reacts with another molecule of ethyl pyruvate bound to the copper(II) center (Fig. 3, left).

This led us to consider how the keto–enol tautomerisation affects the enantioselection of the direct aldol reaction. The keto–enol equilibrium for ethyl pyruvate lies very strongly to the keto form.[39,40] It has been reported that the enol-form rapidily ketonises, although the half life of the enol is amenable to trapping experiments.[41]

Figure 3 (left) shows for the homo-aldol reaction of ethyl pyruvate **1a** (R = Me, R′ = H) the (*Si*)-face approach with the enol-form of **1a** not coordinated to the metal center. This reaction pathway is dependent on the enol concentration in solution. In the limiting case, if there is no enol-form in solution, then this reaction pathway is inhibited. We suggest that if the reaction conditions lead to a very low concentration of the enol-form in solution, then the dominant reaction pathway is the coordinated enol (*Re*)-face approach (Fig. 3, right).

Solvent and counterion properties which will hinder binding of the enol-form of ethyl pyruvate to the copper(II) center will change the reaction path from the (*Re*)-face approach with the enol-form of ethyl pyruvate coordinated to the metal center (Fig. 3, right), to the (*Si*)-face approach (Fig. 3, left). These parameters are (*i*) coordinating counterions such as triflate (OTf), as competitive binding of the triflate to copper(II) will occupy one available binding site at the metal center and (*ii*) a coordinating solvent which can either coordinate to the metal complex and/or stabilize the enol-form in solution. Both of these effects destabilize the intermediate with the enol-form bound to the copper(II), hence promoting the enol-form in solution pathway.

The amines have a significant influence on the enantioselectivity of the reaction as seen in Tables 1, 2 and 4. We propose that for the (*S*)-*t*-Bu-BOX–Cu(II)-catalyzed reactions the coordinating properties of the amines to the metal center are important. To study the effect of amines on the reaction pathways we required 3 different probes: i) a coordinating, non-bulky amine ($CyNMe_2$), ii) a poorly coordinating, non-bulky amine (DMA) and iii) a poorly coordinating, bulky amine (DBA). Comparison of the data from these as additives in the homo-aldol reaction gives us an insight into the transition states. Table 1 shows that the highest enantioinduction by (*S*)-*t*-Bu-BOX–Cu$(OTf)_2$ is obtained when either DMA or DBA is added. Both these amines are poorly coordinating and give significantly better enantioselectivities than for the coordinating amines NEt_3, Et(*i*-Pr)$_2$N and $CyNMe_2$. As DMA and $CyNMe_2$ have similar steric environments at the nitrogen atom we believe the overriding effect causing the decrease in enantiomeric excess from 79% to 50% ee (*cf.* 65% ee when no amine is added) is due to the stronger coordinating property of $CyNMe_2$ affecting the (*Si*)-face attack intermediate (Fig. 3, left). As the homo-aldol reactions in Tables 1,2 are run in Et_2O, with the OTf counterion, this intermediate has already been shown to be dominant.

To analyse the data for the homo-aldol reaction of ethyl pyruvate **1a** in Table 2 a different approach is required. The maximum enantioselectivity for **2a** in Table 2 is 93 and 96% ee, for DBA and DMA, respectively. At these excellent levels of enantioselectivity, it now becomes important to study the effect of product formed *via* the (*Re*)-face attack (Fig. 3, right). Even very small contributions to the product from the (*Re*)-attack will have a dramatic effect on the enantioselectivity at these high levels. The difference between DMA and DBA is due to steric interactions. As high levels of enantioselectivity can be obtained using either of these additives, neither coordinates considerably to the (*Si*)-face attack intermediate (Fig. 3, left). The key difference is if we examine the ability of DMA over DBA to coordinate to the (*Re*)-face attack intermediate and thus destabilize this intermediate. In this case the steric effect is pronounced as DMA can coordinate to the copper center more readily than the bulky DBA. Hence we would expect a lower level of (*Re*)-face attack intermediate when using DMA as compared to DBA, leading to improved enantioselectivity (*i.e.* greater proportion of (*S*)-**2a**). This is shown in Fig. 1 for the amine concentrations 1–7.5 mol% for DMA and DBA. The reason for the lower enantioselectivity for DBA at these amine concentrations is an increased amount of the (*Re*)-face attack intermediate. For DMA the enantioselectivity decreases from 5 mol% to 20 mol% (Table 2, entries 3 and 6), and this is attributed to a sufficient level of DMA to now coordinate to the copper center and perturb the high enantioinduction expected for the (*Si*)-face attack. DBA has a maximum enantioselectivity at 10 mol%. Interestingly, increasing the amount of DBA from 10 to 20 mol% causes a drop in enantioselectivity from 93% to 39% ee! We postulate that the increase in concentration of a poorly-coordinating amine leads to a significant increase in (*Re*)-face attack, even in Et_2O with the OTf counterion. The poorly coordinating, bulky amine DBA affects the intermediates in Et_2O according to many competing factors described above, as illustrated in Fig. 1 by the less defined curve.

Recently, we showed that for Friedel–Crafts reactions catalyzed by the same chiral complex, an amine was co-ordinating to the chiral Lewis acid and having a detrimental effect on the enantioinduction.[16] An improvement in the enantioselectivity of the reaction from 25% to 86% ee was attained by protecting the nitrogen atom of the substrate with bulky protecting groups. 1,3-Dimethoxybenzene also underwent the Friedel–Crafts reaction in 86% ee, confirming the problem with poor enantioinduction was due to coordination through the nitrogen atom.

Since our initial disclosure[11] of the dramatic influence that amine additives invoke on the transition states of chiral BOX–Cu(II) catalyzed reactions, our findings have been useful in optimizing the yield and enantioselectivity in several recent papers.[33,34a,b] In all these cases a study of the effect of amine mol% relative to the catalyst found optimum enantioselectivity was attained when using a 1 : 1 ratio. Catalyst inhibition or poor enantioselectivities occur if different ratios are used. Although expanding the scope of the homo-aldol reaction of ethyl pyruvate proved difficult, we were pleased that the results and conclusions from this work have assisted the development of several important BOX–Cu(II) catalyzed reactions.

Evidence to support our proposed structures in Fig. 3 can also be found from the study of the cross-aldol reactions. The results in Table 6 can be best explained as a poor selectivity of (*Re*)- and (*Si*)-face attack as shown in Fig. 3 (R = CF_3, please observe that the absolute configuration changes due to the CF_3-group).

The absolute configuration of the homo-aldol adduct **2a** based on the two intermediates in Fig. 3 can be extrapolated to the cross-aldol reaction of *e.g.* **1b** with **5**. For R ≠ H, the enol-form is depicted as the *E*-enol isomer, as this has been previously shown to be the reactive form in the related copper(II)-catalyzed asymmetric Mannich reaction between **1b** and α-imino esters[31] and α-amination reactions of **1b** and azodicarboxylates.[32a] As the two products from the different intermediates were diastereoisomers, it was possible to measure the enantioselectivity of each diastereoisomer independently. These results are shown in Table 7 and illustrate how high enantioselectivities are obtained for each diastereomer. This suggests that both proposed intermediates in Fig. 3 induce high degrees of enantioselectivity. The formation of the two different diastereoisomers in Table 7 has given us insight into the different intermediates in Fig. 3 (R = CF_3), and in the homo-aldol reaction of ethyl pyruvate, Fig. 3 (R = CH_3), where only the enantioselectivity is a guide as to the proposed intermediates and their enantioinduction.

Conclusion

The direct catalytic enantioselective aldol reaction of 2-ketoesters has been presented. The aldol reactions can proceed as both a homo- and cross-aldol reaction in the presence of chiral bisoxazoline–copper(II) complexes as the catalyst. The direct homo-aldol reaction of ethyl pyruvate afforded diethyl 2-hydroxy-2-methyl-4-oxoglutarate, which was isolated as the more stable optically active isotetronic acid in good yield up to 96% ee. The enantiomeric excess of the homo-aldol adduct is dependent on the presence of amines and the absolute configuration varies when the counterion is changed from triflate to hexafluoroantimonate The cross-aldol reaction of various 2-ketoesters proceeds with activated carbonyl compounds to give the cross-aldol adduct with excellent enantioselection with up to 96% ee, however, only low diastereoselectivity was obtained. Based on the stereochemical outcome of the reaction, it was proposed that two intermediates are involved in the reaction; one in which the 2-ketoester coordinates to the chiral catalyst in a bidentate fashion with an uncoordinated enolate attacking the activated 2-ketoester. The other intermediate is a pentacoordinated chiral copper(II) complex with both the 2-ketoester and the enolate coordinated to the metal center. These two intermediates can account for the absolute configuration of the aldol adducts obtained in these reactions.

Experimental section

General methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77$) for ^{13}C NMR. Flash chromatography (FC) was carried out using Merck silica gel (230–400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by GC using a Chrompack Chirasil-DEX CB column. The enantiomeric excess of the products was determined by chiral HPLC using a Chiralcel OJ column with hexane/2-propanol as the eluent.

Materials

Ethyl pyruvate **1a**, *N*,*N*-dimethylaniline (DMA), *N*,*N*-dibenzylaniline (DBA), cyclohexyldimethylamine, Hünig's base, imidazole and *N*,*N*-dimethyl-*p*-toluidine (DMT) were purchased from Aldrich and used without further purification. Triethylamine was purchased from Aldrich and distilled over the appropriate drying agent prior to use. Ethyl trifluoropyruvate **5** was purchased from Lancaster and used as received. *N*,*N*-Dibenzyl-*p*-toluidine (DBT) was prepared by benzylation of commercially available toluidine. Ethyl 2-ketobutyrate **1b** was prepared by refluxing 2-ketobutyric acid in ethanol in the presence of a catalytic amount of HCl followed by distillation. 2-Ketoesters **1c**–**f** were prepared in a Grignard reaction of diethyl oxalate and the appropriate bromides following a literature procedure.[43] 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], 2,2′-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline], $Cu(OTf)_2$ and $Zn(OTf)_2$ from Aldrich were stored under an inert atmosphere and used without further purification. $Cu(SbF_6)_2$ was prepared from $CuBr_2$ and $AgSbF_6$ in CH_2Cl_2 in the absence of light and the solution was used for the reaction after filtration through Celite. Solvents were distilled over an appropriate drying agent.

Procedure for formation of compound 4a

To a flame dried Schlenk flask $Cu(OTf)_2$ (36.2 mg, 0.1 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 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 eluent. Solvent was removed *in vacuo* and the residue was re-dissolved in CH_2Cl_2 followed by the addition of dry Et_3N (200 μl, 1.5 mmol) and TBDMSCl (196 mg, 1.3 mmol). The solution was stirred overnight and was purified by FC (SiO_2, 12% Et_2O–pentane) to yield 4-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester as a clear colourless oil.

4-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (4a)

The enantiomeric excess was determined by GC using a Chrompack CP-Chirasil Dex CB (β-PM) column, τ(major) = 20.3 min, τ(minor) = 20.6 min; $[\alpha^{rt}_D] = -84$ ($c = 0.01$, CH_2Cl_2, 96% ee); ^{1}H NMR δ 0.24 (s, 6H), 0.96 (s, 9H), 1.27 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H), 1.69 (s, 3H), 4.21 (q, $^{3}J_{HH}$ = 7.2 Hz, 2H), 6.23 (s, 1H); ^{13}C NMR δ 1.0 (2C), 14.0, 18.3, 22.9, 25.4 (3C), 62.4, 81.7, 124.4, 143.2, 168.1, 169.0; mass (TOF ES$^+$): *m*/*z* 323 (M+Na)$^+$; HRMS calc. for $C_{14}H_{24}NaO_5Si$ 323.1291, found 323.1290.

General procedure for direct catalytic asymmetric crossed aldol reaction of 2-ketoesters (1b–f) with ethyl trifluoropyruvate (5)

To a flame dried Schlenk flask $Cu(OTf)_2$ (0.1 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (0.11 mmol) were added. The mixture was stirred under vacuum for 2–24 h and filled with N_2. Dry solvent (2 ml) was added and the solution was stirred for 2–5 h. *N*,*N*-Dimethyl-*p*-toluidine (0.05 mmol) was added followed by addition of ethyl trifluoropyruvate (2 mmol) and finally the 2-ketoester (1 mmol) was added. The reaction mixture was stirred for the time indicated in Table 8 and was then flushed through a plug of silica with Et_2O as eluent. Solvent was removed *in vacuo* and the residue was redissolved in CH_2Cl_2 followed by the addition of dry Et_3N (3 mmol) and TBSCl (2.6 mmol). The solution was stirred for 24–48 h and was purified by FC (SiO_2, 40% toluene–pentane).

4-(*tert*-Butyl-dimethyl-silanyloxy)-5-oxo-2-trifluoromethyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (4b)

^{1}H NMR δ 0.20 (s, 6H), 0.93 (s, 9H), 1.33 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H), 4.31 (q, $^{3}J_{HH}$ = 7.2 Hz, 2H), 6.13 (s, 1H); ^{13}C NMR δ −3.7 (2C), 13.9, 18.8, 25.8 (3C), 63.8, 109.8, 123.1 (q, $^{1}J_{C,F}$ = 285 Hz) 128.2, 145.9, 163.4, 168.0; mass (TOF ES$^+$): *m*/*z* 377 (M+Na)$^+$; HRMS calc. for $C_{14}H_{21}F_3NaO_5Si$ 377.1008, found 377.1005.

4-(*tert*-Butyl-dimethyl-silanyloxy)-3-methyl-5-oxo-2-trifluoromethyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (4c)

^{1}H NMR δ 0.24 (s, 3H), 0.26 (s, 3H), 0.97 (s, 9H), 1.32 (t, $^{3}J_{HH}$ = 6.8 Hz, 3H), 1.98 (s, 3H), 4.33 (q, $^{3}J_{HH}$ = 6.8 Hz, 2H); ^{13}C NMR δ −4.5, −4.4, 9.5, 13.8, 18.1, 25.4 (3C), 63.6, 116.5, 121.4 (q, $^{1}J_{C,F}$ = 283 Hz), 130.2, 141.6, 162.4, 166.2; mass (TOF ES$^+$): *m*/*z* 391 (M+Na)$^+$; HRMS calc. for $C_{15}H_{23}F_3NaO_5Si$ 391.1165, found 391.1170.

4-(*tert*-Butyl-dimethyl-silanyloxy)-3-cyclohexylmethyl-5-oxo-2-trifluoromethyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (4d)

^{1}H NMR δ 0.24 (s, 3H), 0.28 (s, 3H), 0.78–0.91 (m, 2H), 0.96 (s, 9H), 1.06–1.22 (m, 3H), 1.30 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H), 1.60–1.70 (m, 6H), 2.18 (dd, $^{2}J_{HH}$ = 14.8 Hz, $^{3}J_{HH}$ = 7.2 Hz, 1H), 2.32 (dd, $^{2}J_{HH}$ = 14.8 Hz, $^{3}J_{HH}$ = 7.2 Hz, 1H), 4.28 (q, $^{3}J_{HH}$ = 7.2 Hz, 2H); ^{13}C NMR δ −3.4, −3.2, 14.7, 19.1, 26.4 (3C), 27.0, 27.1 (2C), 33.1, 34.1, 34.3, 36.5, 63.4, 64.5, 122.5 (q, $^{1}J_{C,F}$ = 283 Hz), 133.4, 143.2, 163.9, 167.5; mass (TOF ES$^+$): *m*/*z* 473 (M+Na)$^+$; HRMS calc. for $C_{21}H_{33}F_3NaO_5Si$ 473.1947, found 473.1948.

3-But-3-enyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5-oxo-2-trifluoromethyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (4e)

^{1}H NMR δ 0.28 (s, 3H), 0.29 (s, 3H), 0.98 (s, 9H), 1.32 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 2.26 (q, $^3J_{HH}$ = 7.6 Hz, 2H), 2.41–2.57 (m, 2H), 4.32 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 5.01 (d, $^3J_{HH}$ = 10.0 Hz, 1H), 5.05 (d, $^3J_{HH}$ = 16.8 Hz, 1H), 5.75 (ddt, $^3J_{HH}$ = 6.4 Hz, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 16.8 Hz, 1H); ^{13}C NMR δ −3.5, −3.4, 14.7, 19.0, 24.7, 26.1, 26.3 (3C), 31.5, 64.5, 116.9, 122.3 (q, $^1J_{C,F}$ = 283 Hz), 133.6, 137.2, 143.2, 163.5, 167.2; mass (TOF ES$^+$): *m*/*z* 431 (M+Na)$^+$; HRMS calc. for $C_{18}H_{27}F_3NaO_5Si$ 431.1478, found 431.1473.

4-(*tert*-Butyl-dimethyl-silanyloxy)-5-oxo-3-pentyl-2-trifluoromethyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (4f)

^{1}H NMR δ 0.27 (s, 3H), 0.28 (s, 3H), 0.84–0.89 (m, 5H), 0.96 (s, 9H), 1.27–1.32 (m, 2H), 1.31 (t, $^3J_{HH}$ = 7.6 Hz, 3H), 1.48 (p, $^3J_{HH}$ = 7.2 Hz, 2H), 2.31 (dt, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 8.0 Hz, 1H), 2.41 (dt, $^2J_{HH}$ = 14.8 Hz, $^3J_{HH}$ = 8.0 Hz, 1H), 4.29 (q, $^3J_{HH}$ = 7.2 Hz, 2H); ^{13}C NMR δ −4.4, −4.3, 13.8, 14.1, 18.1, 22.6, 24.3, 25.4 (3C), 26.4, 31.8, 63.5, 121.4 (q, $^1J_{C,F}$ = 280 Hz), 138.4, 141.8, 162.8, 166.4; mass (TOF ES$^+$): *m*/*z* 447 (M+Na)$^+$; HRMS calc. for $C_{19}H_{31}F_3NaO_5Si$ 447.1791, found 447.1797.

4-(*tert*-Butyl-dimethyl-silanyloxy)-3-isobutyl-5-oxo-2-trifluoromethyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (4g)

The enantiomeric excess was determined by HPLC using a Chiralcel OJ column (hexane/*i*-PrOH (97 : 3); flow rate 1.0 ml min^{-1}); τ_{major} = 3.4 min; τ_{minor} = 4.4 min; $[\alpha^{rt}_D]$ = −17.4 (*c* = 1.013 g/l00 mL, $CHCl_3$, 21% ee); ^{1}H NMR δ 0.26 (s, 3H), 0.28 (s, 3H), 0.89 (t, 6H), 0.96 (s, 9H), 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 2.01 (h, $^3J_{HH}$ = 7.2 Hz, 1H), 2.16 (dd, $^2J_{HH}$ = 14.8 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 2.32 (dd, $^2J_{HH}$ = 14.8 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 4.29 (q, $^3J_{HH}$ = 7.2 Hz, 2H); ^{13}C NMR δ −3.4, −3.2, 14.8, 19.1, 23.4, 23.5, 26.4 (3C), 27.3, 34.4, 64.5, 110.7, 122.4 (q, $^1J_{C,F}$ = 283 Hz), 133.6, 143.4, 163.9, 167.5; mass (TOF ES$^+$): *m*/*z* 433 (M+Na)$^+$; HRMS calc. for $C_{18}H_{29}F_3NaO_5Si$ 433.1634, found 433.1632.

Procedure for formation of compound 4ab

To a flame dried Schlenk flask $Cu(OTf)_2$ (0.1 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (0.11 mmol) were added. The mixture was stirred under vacuum for 3 h and filled with N_2. Dry solvent (2 ml) was added and the solution was stirred for 2–5 h. *N*,*N*-dimethylaniline (0.05 mmol) was added followed by addition of ethyl pyruvate (1.0 mmol). The reaction mixture was stirred for 25 h and was then flushed through a plug of silica with Et_2O as eluent. Solvent was removed *in vacuo* and the residue was re-dissolved in CH_2Cl_2 followed by the addition of dry Et_3N (1.13 mmol) and $(t\text{-Bu})_2Si(OTf)_2$ (0.80 mmol). The solution was stirred overnight and was purified by FC (SiO_2, Et_2O–pentane mixture of increasing polarity).

4-(Di-*tert*-butyl-hydroxy-silanyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic acid ethyl ester (4ab)

The enantiomeric excess was determined by HPLC using a Chiralpak AS column (hexane/*i*-PrOH (97 : 3); flow rate 1.0 ml min^{-1}); τ_{major} = 7.0 min; τ_{minor} = 6.2 min; 89% ee; ^{1}H NMR δ 1.03 (s, 9H), 1.04 (s, 9H), 1.26 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.70 (s, 3H), 3.96 (s, 1H), 4.21 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 6.40 (s, 1H); ^{13}C NMR δ 14.9, 27.9 (6C), 23.6 (2C), 28.6, 63.5, 83.6, 126.8, 144.5, 169.4, 170.7; mass (TOF ES$^+$): *m*/*z* 367 (M+Na)$^+$; HRMS calc. for $C_{16}H_{28}NaO_6Si$ 367.1553, found 367.1569.

X-Ray data for 4ab

See reference 42.

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