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Catalytic enantioselective addition of enol silanes to ketomalonate mediated by C_2-symmetric bisoxazoline Lewis acid complexes

Frank Reichel, Xiangming Fang, Sulan Yao, Marina Ricci and Karl Anker Jørgensen*

Center for Metal Catalyzed Reactions, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark. E-mail: kaj@kemi.aau.dk

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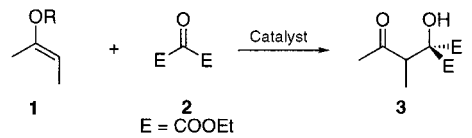
A catalytic enantioselective addition reaction of silyl enol ethers to ketomalonate in the presence of C_2-symmetric copper(II) bisoxazolines as catalysts is presented; the reaction has been studied for different ligands and substrates under various reaction conditions and proceeds in good yield and with ee's > 90% and a procedure for the preparation of an optically active hydroxy acid is shown.

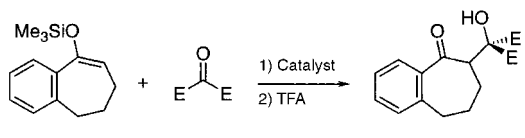
C_2-Symmetric copper(II) bisoxazoline Lewis acid complexes have proven to be highly enantioselective catalysts for a variety of different organic reactions. Such reactions include addition to dicarbonyl compounds[1] where they promote Diels–Alder,[2] hetero-Diels–Alder,[3] Mukaiyama aldol[4] and carbonyl ene reactions.[3a,5] Recently, it has been shown that copper(II) bisoxazolines can catalyze the reaction of ketomalonate with conjugated dienes leading to chiral CO_2 synthons and 1,4-disubstituted cyclohex-2-enes in good yields and ee's > 90%.[1b,6] It was proposed that the reaction proceeded *via* a five-membered ring intermediate with ketomalonate coordinated to the metal center through the reacting carbonyl and one of the two ester carbonyls.[6] This communication presents the first catalytic enantioselective addition of silyl enolates **1** to ketomalonate **2** with high ee in the presence of C_2-symmetric bisoxazoline Lewis acid complexes as the catalysts [eqn. (1)].



(1)

1 **2** (E = COOEt) **3**

Thus, the preparation of highly functionalised molecules such as **3** is achieved in high enantiomeric purity. Compound **3** may be regarded as the starting point for the preparation of valuable compounds such as β-keto and β-hydroxy esters or polyhydroxylated compounds.[7] It should also be mentioned that Evans *et al.*[8] in a very recent paper showed that copper bisoxazolines can also catalyze the enantioselective Michael addition of silylketene acetals to alkylidene malonates. Thus, we were prompted to present our recent results for the reaction outlined in eqn. (2).

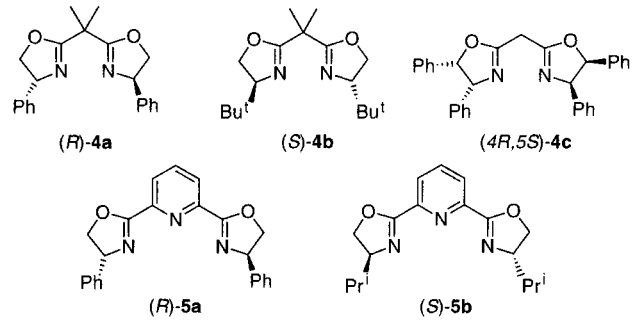


(2)

1a **2** **3a**

The reaction of the silyl enol ether **1a** with ketomalonate **2** has been investigated in order to study the potential of the bidentate and tridentate bisoxazoline-type ligands **4a–c**, **5a**,**b** in combination with $Cu(OTf)_2$ and $Zn(OTf)_2$ as the Lewis acid as enantioselective catalysts.† The yield and ee of **3a** are presented in Table 1.

The results in Table 1 show that both copper(II) and zinc(II) as the Lewis acids in the combination with the various ligands **4a–c**, **5a**,**b** are able to catalyze the reaction of the silyl enol ether



1a with ketomalonate **2**. However, the yield and ee of **3a** are very dependent on the Lewis acid and ligand applied. The highest yields and ee's are obtained with the (*R*)-**4a**-$Cu(OTf)_2$ and (4*R*,5*S*)-**4c**-$Cu(OTf)_2$ (entries 2, 4), where 99 and 94% isolated yield, and 67 and 70% ee, respectively, are obtained. Applying the same ligand, but changing the Lewis acid to zinc(II) leads to a reduction in both yield and ee of **3a** (entry 1). It is notable that changing the chiral ligand from the phenyl-substituted bisoxazoline (*R*)-**4a** to the *tert*-butyl-substituted (*S*)-**4b** and $Cu(OTf)_2$ as the Lewis acid leads to a significant reduction in the ee of **3a** as only 1% ee is obtained (entry 3). The application of the tridentate bisoxazoline ligands **5a**,**b** gives only moderate yield of **3a** accompanied with very low ee's (entries 5,6).

The promising results for the reaction of the silyl ether **1a** with ketomalonate **2** prompted us to investigate the influence of the choice of anions, solvents and temperature on the reaction course. The results are presented in Table 2 and it appears that the reaction is dependent on the solvent, temperature and anion. A fast reaction takes place at room temperature with high isolated yield and 77% ee in Et_2O as the solvent (entries 1–3), while at −10 °C longer reaction times are required to achieve good yield and the best results are obtained in Et_2O and Bu^{t}OMe where 86 and 83% ee are obtained, respectively (entries 5, 6). Changing the anion to hexafluoroantimonate causes a dramatic decrease in ee of **3a** (entry 7). Reducing the reaction temperature to −78 °C improves the ee up to 93% (entry 8). The chiral ligand (4*R*,5*S*)-**4c** is also a promising ligand and similar good yield and high ee are obtained as using (*R*)-**4a**-$Cu(OTf)_2$ as the catalyst (entries 9, 10).

Table 1 The reaction of silyl enol ether **1a** with ketomalonate **2** in the presence of the chiral ligands **4a–c**, **5a**,**b** in combination with $Cu(OTf)_2$ and $Zn(OTf)_2$ as Lewis acid in CH_2Cl_2 at room temperature

Entry	Catalyst	Yield[a] **3a** (%)	Ee[b] (%)
1	(*R*)-**4a**-$Zn(OTf)_2$	65	43
2	(*R*)-**4a**-$Cu(OTf)_2$	99	67
3	(*S*)-**4b**-$Cu(OTf)_2$	87	1
4	(4*R*,5*S*)-**4c**-$Cu(OTf)_2$	94	70
5	(*R*)-**5**-$Zn(OTf)_2$	58	3
6	(*S*)-**5b**-$Zn(OTf)_2$	48	0

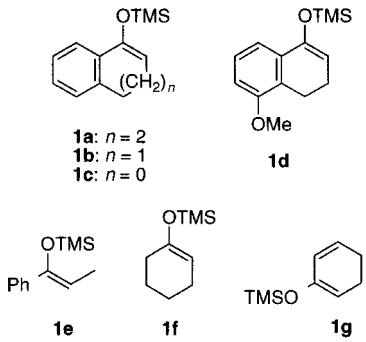
[a] Isolated yield. [b] Determined by chiral HPLC.

Table 2 The reaction of silyl enol ether **1a** with ketomalonate **2** in the presence of the chiral ligands (*R*)-**4a** and (*R*)-**4c** in combination with Cu^{II} salts (10 mol%) in various solvents and different temperatures

Entry	Catalyst	Solvent	*T*/°C	*t*/h	Yield[a] **3a** (%)	Ee[b] (%)
1	(*R*)-**4a**-$Cu(OTf)_2$	CH_2Cl_2	rt	1	99	67
2	(*R*)-**4a**-$Cu(OTf)_2$	Et_2O	rt	1	89	77
3	(*R*)-**4a**-$Cu(OTf)_2$	THF	rt	1	81	71
4	(*R*)-**4a**-$Cu(OTf)_2$	CH_2Cl_2	−10	40	80	78
5	(*R*)-**4a**-$Cu(OTf)_2$	Et_2O	−10	40	81	86
6	(*R*)-**4a**-$Cu(OTf)_2$	Bu^tOMe	−10	40	77	83
7	(*R*)-**4a**-$Cu(SbF_6)_2$	CH_2Cl_2	−10	40	89	37
8	(*R*)-**4a**-$Cu(OTf)_2$	Et_2O	−78	75	88	93
9	(4*R*,5*S*)-**4c**-$Cu(OTf)_2$	CH_2Cl_2	−10	45	94	70
10	(4*R*,5*S*)-**4c**-$Cu(OTf)_2$	Et_2O	−10	40	76	86

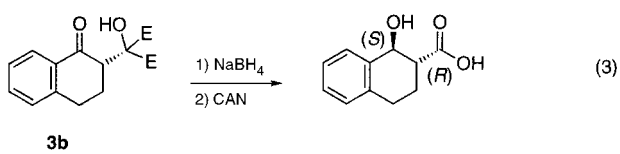
[a] Isolated yield. [b] Determined by chiral HPLC.

The reaction has been studied for a series of silyl enol ethers **1a**–**g** reacting with ketomalonate **2** in the presence of (*R*)-**4a** in combination with $Cu(OTf)_2$ or $Zn(OTf)_2$ and the results are presented in Table 3.



The reactions generally proceed with high isolated yields for the various substrates; for the cyclic aromatic silyl enol ethers **1a**,**b**,**d**, high ee's were obtained (Table 3, entries 1, 3, 6), whereas for the five membered analogue **1c**, the ee is reduced to 58% (entry 5). Furthermore, it appears from the results for **1b**,**c** that zinc(II) also can be used as the Lewis acid, however the ee is lower in these reactions (entries 2, 4). For the aromatic acyclic silyl enol ether **1e** the reaction proceeds also very well with very high isolated yield and ee (entry 7). The cyclic aliphatic silyl enol ether **1f** reacts also smoothly with ketomalonate **2** in the presence of (*R*)-**4a**-$Cu(OTf)_2$ as the catalyst giving the corresponding adduct in good yield and with up to 60% ee (entry 8), whereas the conjugated silyl enol ether **1g** only leads to the corresponding product in moderate yield and ee by using (*R*)-**4a**-$Cu(OTf)_2$ as the catalyst, while high yield and a racemic compound is obtained when (*R*)-**4a**-$Zn(OTf)_2$ is the catalyst (entries 9, 10).

The potential of the reaction is shown by the reduction, followed by oxidative cleavage of the ester groups in **3b** [eqn. (3)] giving the corresponding hydroxy acid in good yield and maintaining the ee obtained in the catalytic step.[9a] These reactions lead also to an assignment of the absolute configuration of the chiral center formed in the catalytic reaction.[9b]



3b (3)

In conclusion we have presented a novel catalytic enantioselective addition reaction of different silyl enol ethers to ketomalonate catalyzed by copper(II) bisoxazoline complexes giving highly functionalized optically active compounds.

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Table 3 The reaction of silyl enol ethers **1a**–**g** with ketomalonate **2** in the presence of (*R*)-**4a**-$Cu(OTf)_2$ or (*R*)-**4a**-$Zn(OTf)_2$ (10 mol%) as the catalyst in Et_2O as the solvent

Entry	Substrate	*T*/°C	*t*/h	Yield[a] (%)	Ee[b] (%)
1[c]	**1a**	−78	75	88	93
2[d,e]	**1b**	−10	42	81	77
3[c]	**1b**	−78	75	91	86
4[d,e]	**1c**	−10	12	91	45
5[c]	**1c**	−78	75	82	58
6[c]	**1d**	−78	65	90	85
7[c]	**1e**	−78	65	95	90
8[c]	**1f**	−78	75	80	60
9[c]	**1g**	rt	18	26	36
10[d]	**1g**	rt	18	96	1

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Catalyst (*R*)-**4a**-$Cu(OTf)_2$. [d] Catalyst (*R*)-**4a**-$Zn(OTf)_2$. [e] CH_2Cl_2 as the solvent.

Notes and references

† *Representative procedure*: $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) and the ligand (*R*)-**4b** (17.6 mg, 0.0525 mmol) were placed in a flame dried Schlenk tube and dried under high vacuum for 1–2 h. Et_2O (1.5 ml) was added and the suspension was stirred for 1 h. Subsequently **2** (76 μl, 0.5 mmol) was added and the mixture was placed in a dry ice–acetone bath and after 30 min **1a** (232 mg, 1.0 mmol) was added. Stirring was continued for 75 h followed by addition of TFA–CH_2Cl_2 (10%, 1 ml). After 30 min TLC showed completion of hydrolysis and the solvent was removed. The residue was purified by FC (20% EtOAc in light petroleum) to afford **3a** (147 mg, 0.44 mmol, 88%) as a colourless oil with 93% ee, determined by chiral HPLC using a Chiralcel OJ column (5% Pr^iOH in hexane, 0.7 ml min^{-1}); $[\alpha]_D^{rt}$ −23.6 (*c* 0.008 g ml^{-1}, $CHCl_3$). δ_H 7.72 (dd, *J* 8.2, 1.1, 1H, arom.), 7.41 (dt, *J* 8.8, 1.5, 1H, arom.), 7.29 (t, *J* 7.2, 1H, arom.), 7.20 (d, *J* 7.1, 1H, arom.), 4.40 (br s, 1H, OH), 4.34–4.20 (m, 4H, CH_2), 3.86 (dd, *J* 11.0, 3.8, 1H, C(O)CHC), 3.12–2.86 (m, 2H, CH_2), 2.17–1.64 (m, 4H, CH_2), 1.28 (t, *J* 7.1, 3H, CH_3), 1.14 (t, *J* 7.1, 3H, CH_3) δ_C 204.4, 170.2, 169.0, 141.6, 137.9, 132.5, 129.9, 129.0, 126.7, 81.3, 62.7, 62.6, 53.5, 32.8, 25.0, 23.7, 14.1, 13.9.

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