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Enantioselective Mukaiyama-Michael Reactions of 2-Carbomethoxy cyclopentenone Catalyzed by Chiral Bis(Oxazoline)-Cu(II) Complexes.

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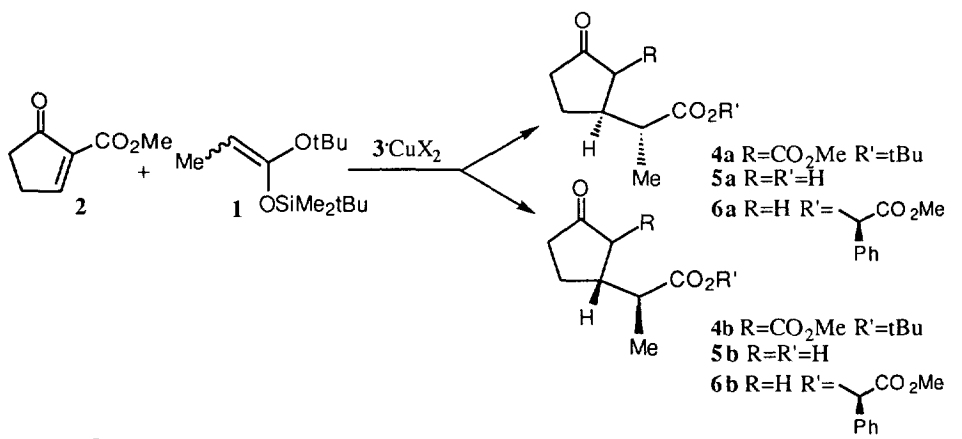
Abstract: The conjugate addition of propionate silylketene acetal **1** to 2-carbomethoxy cyclopentenone is promoted by bis(oxazoline)-Cu(II) complexes with high diastereoselectivity and good enantiomeric excesses. The absolute configuration of the product can be controlled by varying the copper counterion. A catalytic version of the reaction was developed, which gave ketoacid **5a** in 72% d.e. and 63% e.e.

The reaction of Michael-Mukaiyama entails the conjugate addition of enolsilanes to activated double bonds and takes place under the influence of a Lewis acidic activator.[1] Asymmetric versions of this reaction promoted by chiral titanium complexes have been described.[2]

We now disclose that Cu(II) complexes of the bis(oxazolines) **3a-e**[3] (**Figure 1**) are effective promoters for the diastereo and enantioselective conjugate addition of propionate silylketene acetal **1**[4] to 2-carbomethoxy cyclopentenone **2** (**Scheme 1**). Conveniently, either enantiomer of the ketoacid **5** can be obtained by properly choosing the appropriate Cu counterion. The reaction can also be performed using catalytic quantities of the chiral Lewis acid to give the ketoacid **5a** in good diastereomeric and enantiomeric excess.



Scheme 1. Cu(II) bis(oxazoline) promoted Mukaiyama-Michael addition to **2**.

The results of the stoichiometric reactions are collected in the **Table**. One-to-one complexes of the ligands **3a-e** and $Cu(OTf)_2$ or $Cu(SbF_6)_2$ were prepared as described in the literature.[3] After the condensation, the ligands were recovered (≥90%) by filtration on silica gel. The keto diesters **4** were formed with high diastereomeric excess, as judged by ^{13}C NMR of the crude reaction mixtures. The e.e.'s of the major isomer could be measured by ^1H-NMR spectroscopy of **4** in C_6D_6 solution and in the presence of $Eu(hfc)_3$. The stereochemistry at the configurationally labile C_2 position of the cyclopentanone ring was not determined, but the product was treated with refluxing HCl to give the known *syn* ketoacids **5**.[2b,c] In selected cases, the known mandelates **6**[2b, c] were synthesized, a transformation that also established the absolute configuration of the reaction products. The d.e.'s of **6** determined by ^1H-NMR in C_6D_6 solution were found to reproduce the e.e.'s measured on **4**.

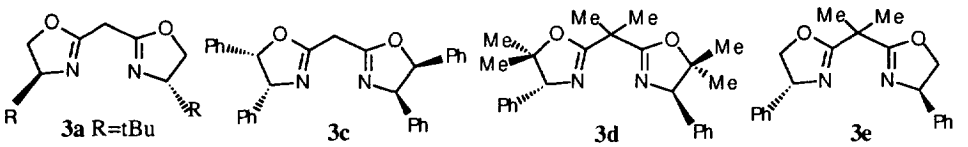


Figure 1. The chiral bis(oxazolines) **3a-e**

Table. CuX_2L^* promoted Mukaiyama-Michael addition of **1** to **2**.[a]

Entry	L*	X	Solvent	Major Isomer	e.e.[b] (%)	Yield (%)	**5** *syn:anti* [c]
1	**3a**	OTf	CH_2Cl_2		0	40	d
2	**3b**	OTf	CH_2Cl_2	**4b**	33	50	d
3	**3c**	OTf	CH_2Cl_2	**4a**	43	50	d
4	**3d**	OTf	toluene	**4a**	58	40	d
5	**3e**	OTf	CH_2Cl_2	**4a**	46	50	d
6	**3e**	OTf	toluene	**4a**	66	63	9:1
7	**3e**	OTf	EtCN	**4a**	28	50	d
8	**3e**	OTf	THF	**4a**	38	33	8.5:1
9	**3e**	SbF_6	toluene	**4b**	11	34	13:1
10	**3e**	SbF_6	CH_2Cl_2	**4b**	60	45	60:1

a. Reactions run for 2h at -78°C in 0.1M solutions, using 1.1 mol equiv of **1** and a stoichiometric amount of promoter. b. Determined by ^1H-NMR of **4** in the presence of $Eu(hfc)_3$ and in C_6D_6 solution. c. Determined by ^{13}C-NMR of **5** or capillary VPC of the corresponding methyl ester. The *anti* isomer is the epimer at either the 3 or 3' position. d. *Syn* isomer only by 200 MHz ^1H-NMR spectroscopy of **5**.

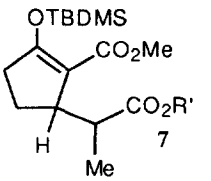
From the data in the **Table**, it is evident that using the $Cu(OTf)_2$ complexes the reaction enantioselectivity is strongly dependent upon the nature of the bis(oxazoline) ligand substituents R^1-R^5 (Entries 1-5). The t-butyl substituted ligand **3a** (Entry 1), which was found to be crucial in order to secure high selectivity in several other reactions,[3, 5] gave a racemic adduct. A modest enantioselectivity (33% e.e., Entry 2) was achieved with the

phenyl substituted bis(oxazoline) **3b**. The presence of two *cis* phenyl groups, as in **3c** (43% e.e., Entry 3), or disubstitution on the methylene bridge, as in **3e** (46% e.e., Entry 5), significantly improved the stereocontrol of the process.

The effects of solvent was studied on the complexes of ligand **3e** (Entries 5-10). Using $Cu(OTf)_2$, the best enantioselectivity was obtained in toluene (66% e.e., Entry 6), which also secured the best chemical yield. Propionitrile (28 % e.e., Entry 7), CH_2Cl_2 (46% e.e., Entry 5), and THF (38% e.e., Entry 8) were all found to be inferior.

A remarkable result was obtained on changing the Cu counterion. Indeed, while starting from the $Cu(OTf)_2$ complex of **3e**, the (3R) cyclopentanone **4a** is obtained (66% e.e., Entry 6), the (3S) enantiomer **4b** is formed in 60% e.e. when the reaction is promoted using $Cu(SbF_6)_2$ as the copper salt (Entry 10). In the latter case, CH_2Cl_2 is found to be the solvent of choice (60% e.e., Entry 10).[6]

In an attempt to further improve the methodology we found that the reaction can be promoted by catalytic quantities of the chiral Lewis acid. Using 0.2 mol equiv of the $Cu(SbF_6)_2$ complex of ligand **3e** in CH_2Cl_2, **4b** is obtained in 11% yield and 65% e.e. along with 48% racemic silylenolether **7**.



Using 0.1 mol equiv of the $Cu(OTf)_2$ complex of **3e** in CH_2Cl_2, the reaction product is an equimolar mixture of **4** and **7**. Upon treatment of this mixture with 1M citric acid in refluxing MeOH to hydrolize **7**, **4a** was isolated in 35% yield and 13% e.e., (compared to 46% e.e. in the stoichiometric reaction, Entry 5). The loss of stereoselectivity in these catalyzed reactions is likely due to the competition of a TBDMSX (X=OTf, SbF_6) promoted addition,[7,8] which affords **7** in racemic form.

Use of a solvent less polar than CH_2Cl_2 is expected to reduce the reactivity of the silyltriflate by inhibiting its dissociation.[9] Indeed, when the conjugate addition was performed with 0.2 mol equiv of the $Cu(OTf)_2$ complex of **3e** *in toluene*, **4a** was formed in 63% e.e. along with minor quantities of the other diastereoisomers (total yield 65%). Racemic **7** was also formed in 25% yield, and easily separated from **4** by flash chromatography. HCl hydrolysis of the crude ketoesters gave the ketoacid **5** with 63% e.e. and 72% d.e. Thus, the catalytic reaction is only slightly less diastereoselective than and just as enantioselective as the stoichiometric process (Entry 6, e.e. 66%, d.e. 80%). To the best of our knowledge, this is the first Mukaiyama-Michael reaction to procede with both diastereo and enantiocontrol under the influence of catalytic quantities of a chiral Lewis acid. Further studies are in course to establish the scope of the method and understand the origin of the observed stereoselectivities.

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References and Footnotes.

1. Oare, D.A.; Heathcock, C.H. *Topics in Stereochem.* **1991**, *20*, 87.
2. a) Kobayashi, S.; Yamada, M.; Mukaiyama, T. *Chem.Lett.* **1994**, 97; b) Bernardi, A.; Karamfilova, K.; Boschin, G.; Scolastico, C. *Tetrahedron Lett.* **1995**, *36*, 1363; c) Bernardi, A.; Karamfilova, K.; Sanguinetti, S.; Scolastico, C. manuscript in preparation.
3. Leading references on the use of these complexes in asymmetric synthesis: a) Evans, D.A.; Miller, S.J.; Lectka, T. *J.Am.Chem.Soc.* **1993**, *115*, 6460; b) Evans, D.A.; Murry, J.A.; von Matt, P.; Norcross, R.; Miller, S.J. *Angew.Chem.Int.Ed.Engl.* **1995**, *34*, 798. c) Corey, E.J.; Imai, N.; Zhang, H.-Y. *J.Am.Chem.Soc.* **1991**, *113*, 728; d) Corey, E.J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807; e) Johannsen, M.; Joergensen, K.A. *J.Org.Chem.* **1995**, *60*, 5757; f) Gothelf, K.V.; Hazell, R.G.; Joergensen, K.A. *J.Org.Chem.* **1996**, *61*, 346; g) Pfaltz, A. *Acc.Chem.Res.* **1993**, *26*, 339; h) Bolm, C. *Angew.Chem., Int.Ed.Engl.* **1991**, *30*, 542; i) Evans, D.A.; Faul, M.M., Bilodeau, M.T.; Anderson, B.A.; Barnes, D.M. *J.Am.Chem.Soc.* **1993**, *115*, 5328; j) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett.* **1991**, 257; k) von Matt, P.; Pfaltz, A. *Angew.Chem., Int.Ed.Engl.* **1993**, *32*, 566; l) Evans, D.A.; Murry, J.A.; Kozlowski, M.C. *J.Am.Chem.Soc.* **1996**, *118*, 5814.
4. Throughout this paper **1** was used as a $\geq$ 9:1 E:Z mixture.
5. Lowenthal, R.E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005; Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta.* **1991**, *74*, 232.
6. A large counterion effect on the levels of stereoselectivity (but not on the sense of induction) was previously reported for some bis(oxazoline)-Cu(II) catalyzed Diels-Alder reactions (*ref. 3b*). We speculate that in our case the inversion of stereoselectivity observed passing from X=OTf to X=SbF_6 may arise from a different coordination geometry around the metal ion.
7. Addition of **1** to **2** in the presence of 1 mol equiv of TBDMSOTf occurs in 2h at -78°C, to yield a mixture of **4** and **7**.
8. It is known that TDBMSCl is not a promoter for the addition of **1** to **2** (*ref. 2b,c*). However, using $CuCl_2$ as the copper salt, the resulting complex with **3e** was poorly soluble in CH_2Cl_2 and did not behave as an effective promoter.
9. For a discussion of silyltriflate catalyzed Mukaiyama reactions see: Hollis, K.T.; Bosnich, B. *J.Am.Chem.Soc.* **1995**, *117*, 4570.

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