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SHORT COMMUNICATION

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A General Asymmetric Aldol Reaction of Silyl Ketene Acetals Derived from Simple Esters to Aryl alpha-Ketoesters

Julie Le Engers,[a] and Brian L. Pagenkopf[b]*

Keywords: aldol / bis(oxazoline) / Asymmetric catalysis / Synthetic methods / alpha-Ketoesters

A general method for the enantioselective addition of O,O-ketene silyl acetals made from simple esters to alpha-kesters catalyzed by a $CuCl_2$•bis(oxazoline) complex is reported that overcomes the limitations of the classic aldol reaction, such as steric intolerance and the need for expensive thio esters. This method excels with aryl alpha-ketoesters and provides products in good yield and high ee that are not readily available by alternative strategies.

(© WILEY-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

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Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

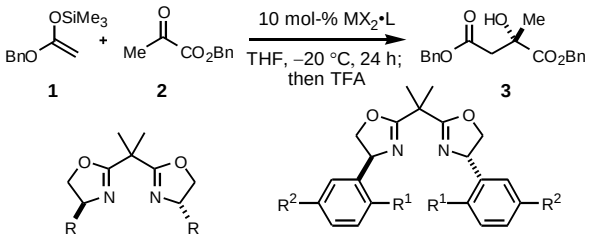
Introduction

The Evans enantioselective addition of silyl enol ethers of thioesters to α-ketoesters catalyzed by copper(II) bis(oxazoline) complexes stands as a landmark achievement in aldol chemistry.[1,2] However, the process is sensitive to sterics and even diminutive changes to the thioester nucleophile or α-ketoester structures can result in a significant drop in *ee*.[3] The thioesters, which are required for good enantioselectivity, are about a thousand times more expensive than simple esters.[4] The importance of methods for the preparation of chiral quaternary centers has driven the development of new synthetic transformations employing α-ketoesters as substrates which overcome many of the aforementioned limitations. For example, closely related methods include the asymmetric addition of enol silanes to α-ketoesters using a Ag(I) catalyst as reported by Snapper and Hoveyda,[5] and by Bolm using sulfoximines in a Cu(II) catalyzed system.[6] Additionally, asymmetric Henry reactions,[7] ene reactions,[8] reductive couplings,[9] reductions[10] and alkyl zinc additions[11] with α-ketoesters have been reported.[12] Recently, we described new copper(II) catalysts made from substituted aryl bis(oxazoline) ligands that addressed some of the steric and electronic limitations of α-ketoesters in aldol reactions with silyldienolates.[13,14] In this communication a general method for the enantioselective addition of *O,O*-ketene silyl acetals made from simple esters to α-ketoesters catalyzed by a $CuCl_2$•bis(oxazoline) complex is reported that overcomes the limitations of the classic aldol reaction (*vide supra*), and provides products in good yield and high *ee* that are not readily available by alternative methods.[15,16,17,18]

Results and Discussion

The investigation began with screening a variety of Lewis acids that have been used in Mukaiyama aldol reactions (Table 1), with silyl ketene acetal **1** and benzyl pyruvate **2** selected as model substrates. With our ligand **L3**[13] the best catalyst performance was observed with a $CuCl_2$ catalyst system (entry 9).[19,20,21]

Table 1. Lewis Acid screening for aldol reaction of silyl ketene acetal **1**

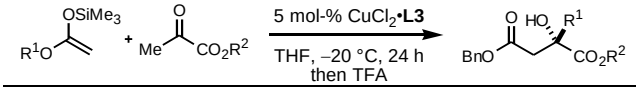


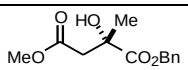
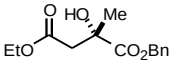
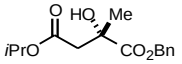
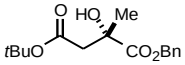
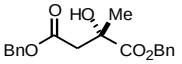
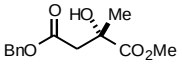
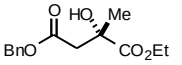
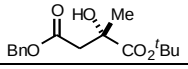
Entry	Ligand	Lewis acids	*ee* (%)	Yield (%)
1	**L1**	$Cu(OTf)_2$	65	93
2	**L2**	$Cu(OTf)_2$	31	52
3	**L3**	$Cu(OTf)_2$	35	78
4	**L3**	$Cu(SbF_6)_2$	16	78
5	**L3**	$Mg(OTf)_2$	11	10
6	**L3**	$Zn(OTf)_2$	14	79
7	**L3**	$Sn(OTf)_2$	10	21

8	**L3**	$Sc(OTf)_3$	7	82
9	**L3**	$CuCl_2$	94	84

The results in Table 2 entries 1 – 5 show that the product *ee* is dependent on the size of the ester, with a small methyl substituent giving the lowest *ee* at 71%, and both *t*Bu and benzyl giving 94% *ee*. A similar trend was observed with the pyruvate component Table 2 (entries 5 – 8), where increasing the size of the alkoxy pyruvate component from Me or Et to Bn gave *ee*'s of 89%, 91% and 94% respectively. There was no reaction with the *t*Bu substrate, presumably due to steric constraints. Currently, substituted silylketene acetals are not successful.

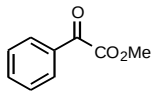
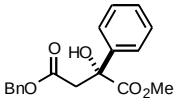
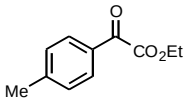
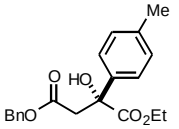
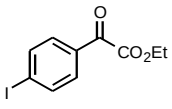
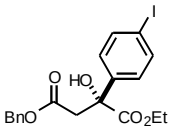
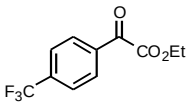
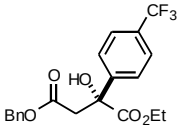
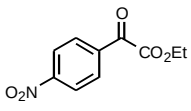
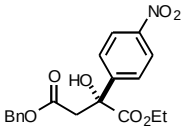
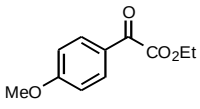
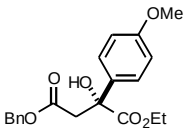
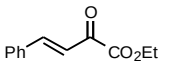
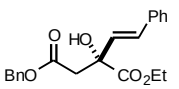
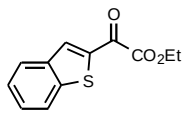
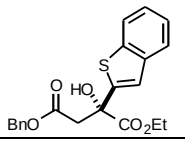
Table 2. Reaction Scope with Systematic Steric Variations



Entry	R^1	R^2	Product	*ee* (%)	Yield (%)
1	Me	Bn		71	65
2	Et	Bn		88	71
3	*i*Pr	Bn		91	67
4	*t*Bu	Bn		94	58
5	Bn	Bn		94	88
6	Bn	Me		89	84
7	Bn	Et		91	85
8	Bn	*t*Bu		–	no rxn

Having observed such unusual steric tolerance, the reaction scope was further explored. We were delighted to find that the reaction could be extended to aryl α-ketoesters, and excellent enantioselectivities (92 – 97% *ee*) were observed for electronically neutral or activated electron deficient arenes (Table 3, entries 1 – 5), including those with halogen (entry 3) and nitro (entry 5) functional handles. With an electron donating methoxy group (entry 6) no reaction was observed, presumably due to attenuated ketone electrophilicity. Also, unsaturated glyoxylates (entry 7) afforded good enantioselectivities (97% *ee*). Entry 8 demonstrates compatibility with benzothiophene containing substrates as well (94% *ee*). It should be noted that the *ee*'s reported here are superior to those observed for the addition of dienosilane to glyoxylates.[13]

Table 3. Asymmetric Aldol Addition of Aromatic Glyoxylate Esters

Entry	Glyoxylate	Product	*ee* (%)	Yield (%)
1			96	80
2			97	75
3			92	81
4			95	83
5			96	73
6			–	no rxn
7			97	80
8			94	78

The results with aliphatic glyoxylate esters summarized in Table 4 are promising, but not as impressive as the selectivities observed with aryl glyoxylates. Using **L3** as the chiral ligand, the best selectivity was found to be 89% *ee* when R^1 is a methyl (Table 2, entry 6), but by increasing the size of R^1 to ethyl the *ee* dropped to 65% (Table 4, entry 1). Further increasing the size of the alkyl group to *n*hexyl, *i*butyl or *i*propyl gave *ee*'s of 62%, 54% and 35%, respectively. However, significant improvement was observed when **L4** was employed (see Table 1 for structure, Figure 1 for X-ray), giving useful *ee*'s ranging from 85% to 70% for the ethyl to isopropyl series (Table 4, entries 1 – 4).[22]

Table 4. Asymmetric Aldol Addition of Aliphatic Glyoxylate Esters

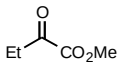
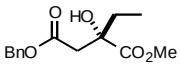
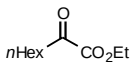
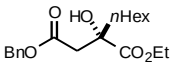
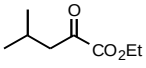
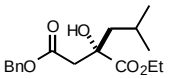
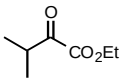
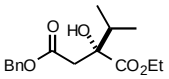
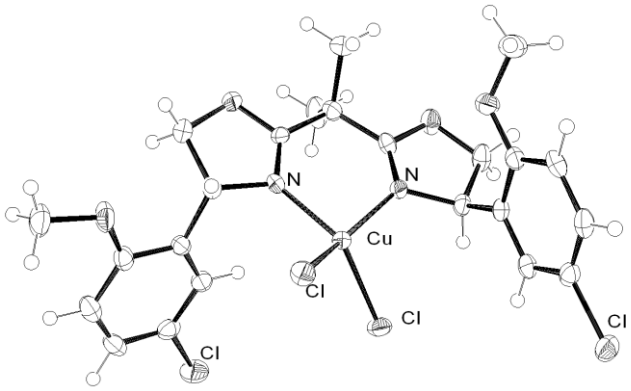
Entry	Pyruvate	Product	Ligand % *ee* (% Yield)	
			L3	L4
1			65 (70)	85 (75)
2			62 (63)	85 (68)
3			54 (70)	80 (70)
4			35 (62)	73 (75)

Figure 1. X-ray structure of complex L4.



Conclusions

The asymmetric aldol reactions of silyl ketene acetals of inexpensive esters and aryl glyoxylates has been reported. This catalyst system is more tolerant to structural variation of the substrates than the corresponding thioester aldols. Moreover, this method excels with aryl α-ketoesters and is therefore highly complementary to other synthetic strategies.

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Published online: ((will be filled in by the editorial staff))

Supporting Information Available: General experimental procedures and characterization of all new compounds, an X-ray structure of **L4**, and copies of NMR spectra.

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[3] For example, methyl pyruvate gave 99% *ee*, whereas ethyl pyruvate gave 91% *ee*.

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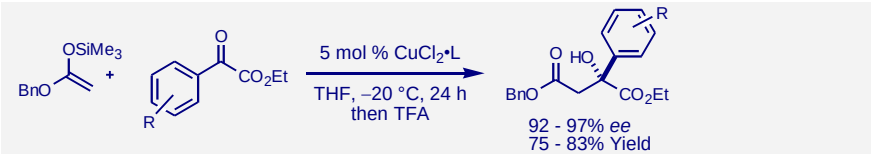
[21] The role that the aryl substituents play on the selectivity of the reaction is currently unknown.

Entry for the Table of Contents

Layout 2:



The asymmetric aldol reaction of silyl ketene acetals of simple esters to alpha-ketoesters is reported. The reaction is tolerant of substrate variation and excels with aryl alpha-ketoesters. The process uniquely employs inexpensive esters rather than costly thioesters.

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A General Asymmetric Aldol Reaction of Silyl Ketene Acetals Derived from Simple Esters to Aryl alpha-Ketoesters

Keywords: aldol / bis(oxazoline) / Asymmetric catalysis / Synthetic methods / alpha-Ketoesters