Asymmetric Catalysis

DOI: 10.1002/anie.201402233

Highly Enantioselective Carbonyl–Ene Reactions of 2,3-Diketoesters: Efficient and Atom-Economical Process to Functionalized Chiral α-Hydroxy-β-Ketoesters**

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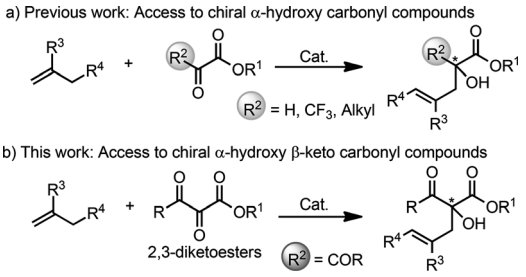
Abstract: *Carbonyl–ene reactions of 2,3-diketoesters catalyzed by [Cu{(S,S)-tBu-box}](SbF$_6$)$_2$ [box = bis(oxazoline)] generate chiral α-functionalized α-hydroxy-β-ketoesters in up to 94% yield and 97% ee. The 2,3-diketoesters are conveniently accessed from the corresponding α-diazo-β-ketoester, and a catalyst loading as low as 1.0 mol% can be achieved.*

The carbonyl–ene reaction is a versatile, atom-economical process for carbon–carbon bond formation.[1] Since the first asymmetric examples of this reaction reported by Yamamoto and co-workers,[2] numerous chiral Lewis[3–7] or Brønsted[8] acid catalytic systems have been successfully developed. With few exceptions,[4,5] glyoxylate systems have been the sole carbonyl substrates in the development of asymmetric carbonyl–ene reactions because they are highly activated, allow bidentate coordination to the catalyst, and provide access to functionalized chiral α-hydroxyacetates. Trifluoroacetyl ketone analogues have recently received considerable attention (Scheme 1 a, R^2 = CF$_3$),[4,8a–c] but there are only two

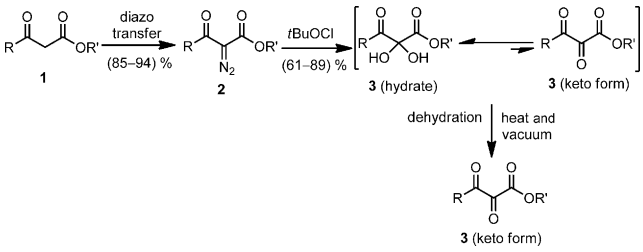


Scheme 1. Asymmetric carbonyl–ene reactions.

reports in which an alkyl substituent has been installed at the α-position.[5] Because of very long reaction times, which are required with pyruvates,[5a] or the need to use a highly activated enolsilyl counterpart to decrease reaction times,[5b] the impression given by these reports is that effective asymmetric carbonyl–ene reactions are restricted to glyoxylates,[1] and that the development of a general, asymmetric process which extends the complexity and functionality of the product is a challenging task.

Recently our group has used 2,3-diketoesters in catalytic approaches to the highly selective syntheses of functionalized furans and cyclopentanones.[9] Because of its multiple coordinating sites and the highly reactive electrophilic character of the central carbonyl group, we envisioned that 2,3-diketoesters would be excellent candidates for carbonyl–ene reactions. Herein, we report the broadly applicable catalytic asymmetric carbonyl–ene reactions, of 2,3-diketoester derivatives, which occur with high yield and enantiocontrol (Scheme 1 b). This strategy allows the formation of functionalized chiral α-hydroxy-β-ketoesters, an important structural motif found in biological molecules, drug candidates, and key intermediates in natural product synthesis.[10] Although the 2,3-diketoester functional group has been used for many years in the synthesis of numerous examples of carbocyclic compounds, heterocycles, and natural products,[11] this is the first demonstration of its viability in a catalytic asymmetric transformation.

The preparation of 2,3-diketoesters (**3**) is achieved by a variety of known methods.[11b] In our investigations, these derivatives were readily obtained as hydrates in high yield through diazo transfer to 1,3-dicarbonyl compounds with subsequent dinitrogen replacement by oxygen using *tert*-butyl hypochlorite (Scheme 2).[11b] Although oxidation of α-diazo-



Scheme 2. Preparation of 2,3-diketoester derivatives.

β-ketoesters to 2,3-diketoesters was achieved in excellent to quantitative yield using dimethyldioxirane,[9] for large-scale reactions the commercially available *tert*-butyl hypochlorite oxidant is more practical. The 2,3-diketoesters **3** exist predominantly as the hydrate in equilibrium with the keto form, but the keto form is easily obtained (see the Supporting Information) by heating (90–100 °C) the hydrate under vacuum for 10 minutes (Scheme 2).

Evans and Wu previously reported that the chiral scandium(III) bis(oxazolinyl)pyridine (pybox)[7e] complex

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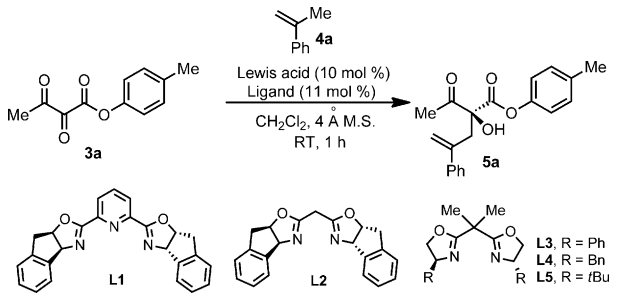
[**] Support for this research from the National Science Foundation (CHE 1212446) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201402233.

was an effective catalyst for highly enantioselective carbonyl–ene reactions. As the success of this process was proposed to result from the rigidity of the coordinated substrate as a result of two-point binding, we thought this catalyst system would also be suitable for high enantiocontrol in reactions with 2,3-diketoesters. However, reaction of **3a** with α-methylstyrene (**4a**), catalyzed by scandium(III)[7e] triflate ligated with pybox (**L1**), generated the product **5a** with only 18% *ee* (Table 1, entry 1). However, this outcome was surprising in view of prior reports of the slow conversions of keto analogues of glyoxylates,[5a] as the reaction was complete within 1 hour at room temperature (entry 1). Encouraged by this result, we examined reactions with other Lewis acid/chiral ligand catalysts and discovered that bidentate chiral copper(II) bis(oxazoline) (box) complexes, which had been previously employed in asymmetric carbonyl–ene reactions[3d,5a] with glyoxylates, were optimum. The best results were obtained using $Cu(OTf)_2$[3d] or $Cu(SbF_6)_2$[5a] ligated with **L5** (entries 2 and 3). With the chiral box ligands **L2**–**L4** and $Cu(SbF_6)_2$, comparable activity was found, but the carbonyl–ene product was formed with lower *ee* values (entries 4–6). Changing the solvent to THF and CH_3CN resulted in only trace amounts of product, whereas DCE and toluene provided similar results to those obtained with CH_2Cl_2 (entries 7–10). Since $Cu(SbF_6)_2$ ligated with **L5** provided the highest yield and *ee* value, this catalytic system was selected for further optimization.

Table 1: Catalyst screening and optimization of reaction conditions.[a]

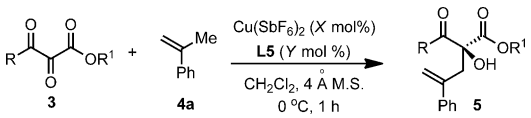


Entry	Lewis acid	Ligand	Solvent	Yield [%][b]	*ee* [%][c]
1	$Sc(OTf)_3$	**L1**	CH_2Cl_2	91	18
2	$Cu(OTf)_2$	**L5**	CH_2Cl_2	90	70
3	$Cu(SbF_6)_2$	**L5**	CH_2Cl_2	92	75
4	$Cu(SbF_6)_2$	**L2**	CH_2Cl_2	68	58
5	$Cu(SbF_6)_2$	**L3**	CH_2Cl_2	84	65
6	$Cu(SbF_6)_2$	**L4**	CH_2Cl_2	89	28
7	$Cu(SbF_6)_2$	**L5**	THF	trace	–
8	$Cu(SbF_6)_2$	**L5**	CH_3CN	trace	–
9	$Cu(SbF_6)_2$	**L5**	DCE	87	74
10	$Cu(SbF_6)_2$	**L5**	toluene	84	65

[a] Reactions were carried out on a 0.25 mmol scale of **3a** (keto form) with 3.0 equiv of α-methylstyrene (**4a**) in 2.0 mL of solvent at room temperature. [b] Yield of product isolated after after column chromatography. [c] Determined by chiral-stationary-phase HPLC analysis. DCE = 1,2-dichloroethane, M.S. = molecular sieves, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl.

A variety of aryl and alkyl ester derivatives (**3**) were examined to determine the influence of structure on enantioselectivity, but they had only minimal impact (Table 2, entries 1–6). However, product yields were significantly impacted with R^1 = Me and *t*Bu. However, modification of the 3-keto unit from acetyl (**3c**) to propanoyl (**3f**) increased the enantioselectivity from 82% to 92% (entry 7) without diminishing the product yields. Catalyst loading could be decreased to 1 mol% using longer reaction times, without effecting either the yield or enantioselectivity (entries 8 and 9). Enantioselectivities were further improved to 94% when the reaction was performed at −78°C and then slowly warmed to 0°C (entry 10). To test the reproducibility of this process, a gram-scale reaction was performed with **3g**, and the α-hydroxy-β-ketoester **5g** was obtained in 88% yield with 94% *ee* (entry 11). Remarkably, the readily accessible hydrate form of **3g** could also employed in the catalytic asymmetric carbonyl–ene process, thus producing **5g** with similar yield and *ee* value upon isolation after a 24 h reaction time, as compared to a 1 hour reaction time needed for the keto form **3g** (entry 12 versus entry 10). Use of the hydrate rather than the keto form is obviously only a limitation in reaction time.

Table 2: Exploring the substituent effects on yield and selectivity with 2,3-diketoesters.[a]

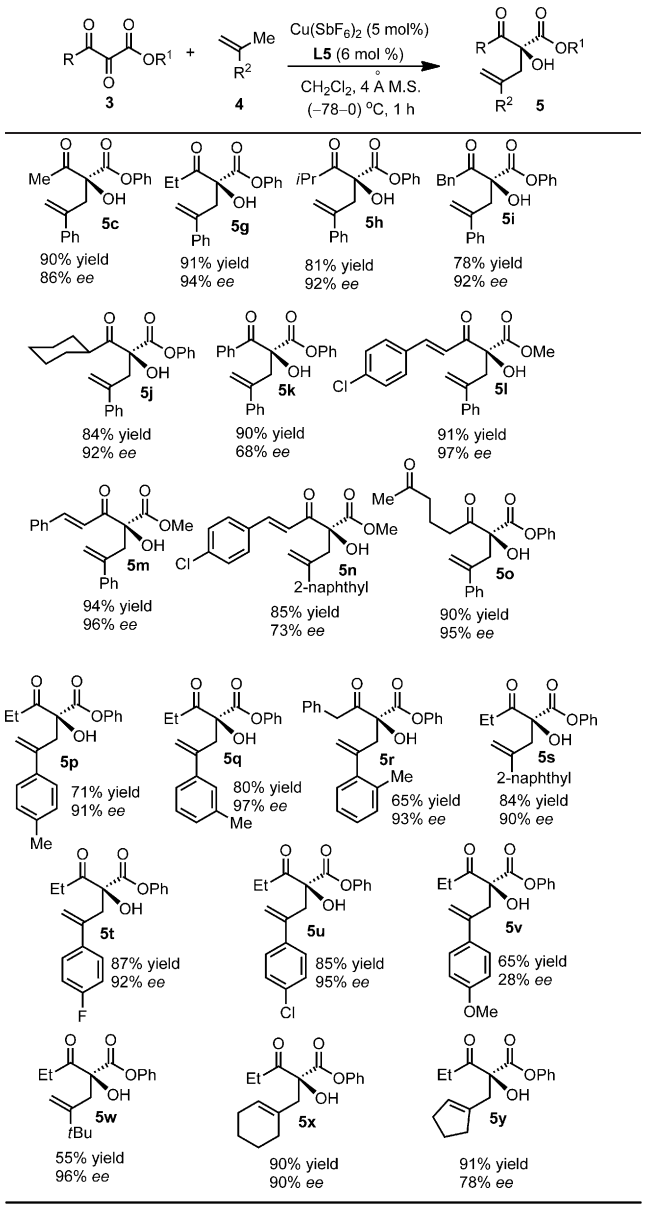


Entry	3	5	mol% Catalyst[b]	R	R^1	Yield [%][c]	*ee* [%][d]
1	**3a**	**5a**	10	Me	4-MeC_6H_4	92	80
2	**3b**	**5b**	10	Me	4-ClC_6H_4	91	83
3	**3c**	**5c**	10	Me	Ph	90	82
4	**3d**	**5d**	10	Me	Bn	90	82
5	**3e**	**5e**	10	Me	Me	64	85
6	**3f**	**5f**	10	Me	*t*Bu	58	86
7	**3g**	**5g**	10	Et	Ph	91	92
8	**3g**	**5g**	5	Et	Ph	91	92
9[e]	**3g**	**5g**	1	Et	Ph	90	92
10[f]	**3g**	**5g**	5	Et	Ph	91	94
11[f,g]	**3g**	**5g**	5	Et	Ph	88	94
12[h]	**3g**	**5g**	5	Et	Ph	87	91

[a] Reactions were carried out on a 0.25 mmol scale of **3** (keto form) with 3 equiv of α-methylstyrene (**4a**) in 2.0 mL of solvent, unless noted otherwise. [b] X mol% as listed; Y = 1.2 times X. [c] Yield of product after chromatographic purification. [d] Determined by chiral-stationary-phase HPLC analysis. [e] Reaction was stirred for 3 h. [f] Reaction was performed at −78°C then slowly warmed to 0°C. [g] Reaction was carried out on a 5.0 mmol scale of **3g**. [h] The hydrate form of **3g** was used, and the reaction was run for 24 h.

Reactions between the structurally diverse 2,3-diketoesters **3** and various alkenes **4** were examined under optimized reaction conditions (Table 3). The alkyl (R) substituents of **3**, including methyl, ethyl, isopropyl, benzyl, and cyclohexyl, reacted smoothly with α-methylstyrene to generate **5c** and **5g–j** in high yield and enantioselectivity. However, enantiomeric excess fell to 68% when R = phenyl (**5k**). To further expand the reaction scope of the 2,3-diketoesters **3**, additional functionalities (R) were explored. Reactions of **3** (R = styryl derivatives) with α-methylstyrene provided **5l** and **5m**, respectively, in excellent yield and enantiomeric access. The

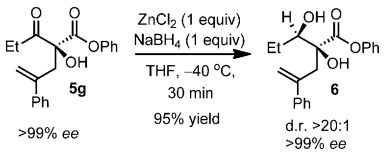
Table 3: Substrate scope of carbonyl–ene reactions with 2,3-diketoesters.



successes achieved with these substrates further demonstrate the generality of the ene reactions with 2,3-diketoesters and their applicability in forming products containing the α,β-unsaturated carbonyl functionality, which is suitable for further chemical transformations. The carbonyl–ene reaction is also compatible with **3** where the R substituent is an alkyl chain containing a keto functional group; the product from this reaction (**5o**) was generated in 90% yield and 95% *ee*. In contrast to the high *ee* value obtained with α-methylstyrene, however, reaction of **3** (R = styryl) with the naphthyl analogue 2-isopropenylnaphthalene produced **5n** in only 73% *ee*.

Examination of the reactions of the 2,3-diketoester **3** with various alkenes **4** further demonstrated the broad applicability of this methodology. High yields and excellent *ee* values were obtained for aromatic alkenes containing weak electron-donating, electron-withdrawing, and halogen substituents (**5p–u**), although the *o*-Me substituent caused a decrease in product yield. However, as seen in the outcome for **5v**, the methoxy substituent dramatically decreased both the yield and *ee* value.[3j] Acyclic alkenes and methylenecycloalkanes are also suitable, thus forming **5w** and **5x** in high yield and *ee* value, but there was a slightly lower *ee* value with methylenecyclopentane **5y** compared to methylenecyclohexane.

To demonstrate their utility, the keto group was reduced by sodium borohydride in the presence of $ZnCl_2$ at −40 °C in high yield with complete diastereoselectivity, thus producing the enantiomerically pure (2*S*,3*R*)-vicinal diol **6** bearing a tertiary carbinol (Scheme 3). This structural motif has played an essential role in natural products synthesis.[12]



Scheme 3. Stereoselective reduction of the α-hydroxy-β-ketoester **5g**.

The absolute configuration of **5** was determined to be *S* through single-crystal X-ray analysis of **5n** (Figure 1a). The relative stereochemistry of **6** was determined by ^{1}H NMR nOe experiments with the corresponding protected diol **7** (Figure 1b).

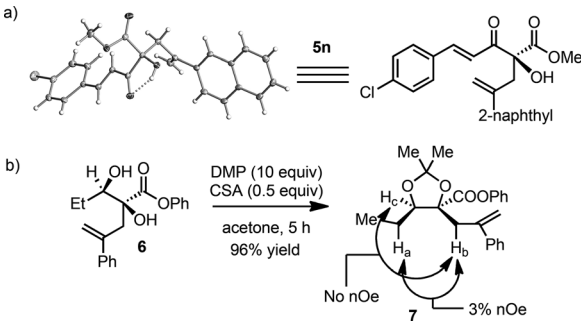


Figure 1. a) X-ray crystal structure of **5n** from asymmetric carbonyl–ene reaction. b) NOE experiment of the acetonide **7**. CSA = camphor-10-sulfonic acid, DMP = 2,2-dimethoxypropane.

We have previously proposed Lewis acid activation of the central carbonyl of 2,3-diketoesters through a bidentate coordination with the more basic keto group rather than with the carboxylate group,[9b] and our current data provides further evidence for this claim. If the [Cu{(*S*,*S*)-*t*Bu-box}]-$(SbF_6)_2$ catalyst undergoes bidentate coordination with the 2,3-diketoester **3** in a square-planar complex,[13] so that the central carbonyl oxygen atom and the adjacent keto carbonyl are bound (**8**), the approach through the *Si* face is sterically hindered by the *tert*-butyl substituent of the box ligand, thus allowing olefin approach from only the *Re* face, and thus generates the *S* enantiomer (Figure 2). In contrast, if bidentate coordination of the catalyst occurred with the central

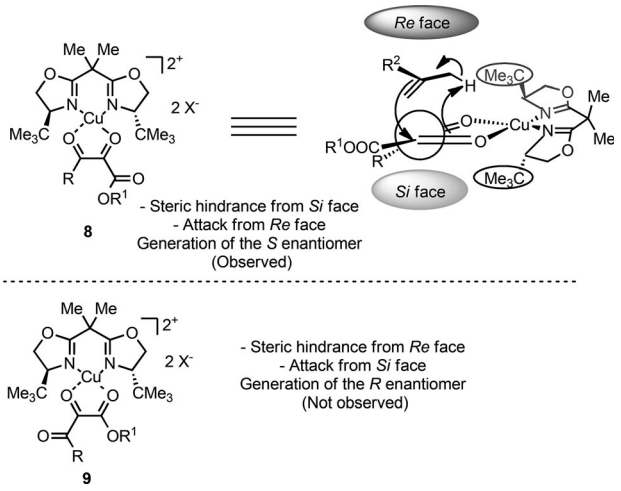


Figure 2. Activation of phenyl 2,3-diketopropionate by [Cu{(*S*,*S*)-*t*Bu-box}]$(SbF_6)_2$.

carbonyl oxygen atom and the ester carbonyl (**9**), olefin attack would come from the less sterically hindered *Si* face to generate the *R* enantiomer. Since, the *S* enantiomers are formed in this carbonyl–ene reaction, the ligated copper catalyst most likely forms bidentate complexes with the two keto carbonyls of the 2,3-diketoesters system (**8**). Complexation of the 2,3-diketoester **3g** with [Cu{(*S*,*S*)-*t*Bu-box}]-$(SbF_6)_2$ was further verified by the spectral shift in the visible region of the electromagnetic spectrum from the titration experiment of the chiral copper complex with **3g** (Figure 3). Although the six-membered ring bidentate chelation of oxazolidinones to copper(II)/(box) has been well studied,[13] observation of the complexation of 2,3-diketoesters which form five-membered ring chelates was not previously confirmed.

In conclusion, a general, highly enantioselective carbonyl–ene reaction using 2,3-diketoester derivatives significantly broadens the scope of this useful transformation and extends

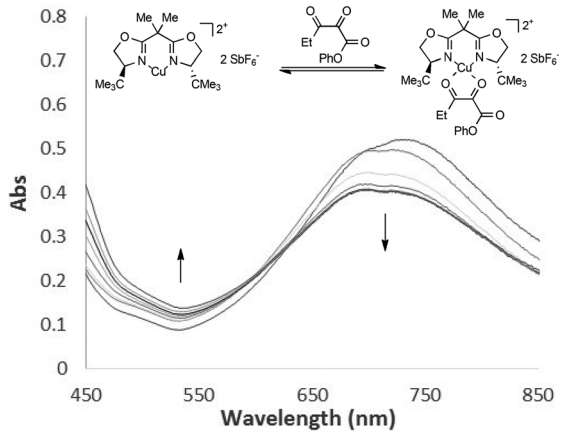


Figure 3. Sequential aliquots of the 2,3-diketopropionate **3g** (0.1 equiv–2.0 equiv) were added to a solution of [Cu{(*S*,*S*)-*t*Bu-box}]-$(SbF_6)_2$ (20×10^{-3} mmol) in 2.5 mL CH_2Cl_2, and thus provided a well-defined isosbestic point at $\lambda = 592$ nm with an incremental shift of λ_{max} from 750 nm to 680 nm.

access to chiral α-substituted α-hydroxy-β-ketoesters beyond that currently available.[10f–h] The placement of diverse functional groups, at the α-position, which are suitable for subsequent transformations, is of particular value for the construction of enantiomerically enriched synthetic intermediates for natural products.[10e,i] Furthermore, the demonstration of their high stereoselectivities in asymmetric ene reactions suggest that 2,3-diketoesters should also be susceptible to other nucleophiles in an asymmetric fashion. Further studies with other nucleophiles are in progress.

Experimental Section

General procedure for the synthesis of functionalized α-hydroxy-β-ketoesters (**5**): A solution of the 2,3-diketoester **3** (0.25 mmol, 1.0 equiv), after dehydration of the hydrate and 120 mg of 4 Å molecular sieves in 1.75 mL of CH_2Cl_2 under a nitrogen atmosphere, was cooled to −78 °C. Then 0.25 mL (0.050 M) of the chiral catalyst solution and alkene **4** (0.75 mmol, 3.0 equiv) were added sequentially. The reaction was stirred for 10 min at −78 °C, then transferred to an ice bath and stirred for additional 50 min. The reaction mixture was directly subjected to flash column chromatography (SiO_2) eluting with hexanes and ethyl acetate to provide the pure product **5**.

Received: February 9, 2014
Revised: March 12, 2014
Published online: May 20, 2014

Keywords: asymmetric catalysis · carbonyl–ene reaction · copper · ligand effects · synthetic methods

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