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Highly Enantioselective Conjugate Addition of Cyclic Diketones to β,γ-Unsaturated α-Ketoesters Catalyzed by an *N,N′*-Dioxide-Cu(OTf)$_2$ Complex**

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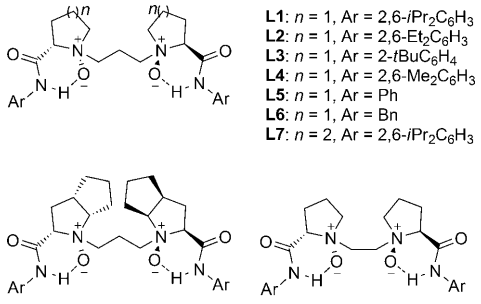
As one of the most powerful tools for the formation of carbon–carbon bonds in organic synthesis, the catalytic asymmetric Michael reaction has been the subject of intensive development.[1] Among various types of Michael donors and acceptors, the addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds has received increased attention, since the addition products have promising biological and pharmaceutical activities.[2,3] Potentially, the reaction could follow a cascade acetalization to construct a six-membered oxygenated heterocycle; one of the most common natural product frameworks, which exhibit an extensive array of biological activities.[4] Compared with α,β-unsaturated aldehydes and ketones, reactions with β,γ-unsaturated α-ketoesters as Michael acceptors are limited.[5] Since the pioneering work of Jørgensen and co-workers,[6a] there have been several reports, for example, from the groups of Xu and Zhao, of enantioselective conjugate addition reactions of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-ketoesters.[6c,d] However, the application of cyclic diketones as nucleophiles is yet to be investigated. Recently, Calter and Wang have described a highly asymmetric conjugate addition reaction of cyclic diketones to β,γ-unsaturated α-ketoesters using a cinchona alkaloid derivative. They obtained excellent yields and enantioselectivites and the product was easily transformed into a hexahydroquinoline.[6b] Considering the high synthetic versatility of the products, the development of more efficient approaches for the enantioselective conjugate addition of cyclic diketones with β,γ-unsaturated α-ketoesters remains challenging and in high demand. Herein, we report a highly enantioselective conjugate addition of cyclic diketones to β,γ-unsaturated α-ketoesters using an *N,N′*-dioxide/Cu(OTf)$_2$ catalyst complex. With a catalyst loading of 2 mol% excellent yields (up to 99%) and enantioselectivities (up to 99% *ee*) were obtained for a wide range of substrates.

Chiral *N,N′*-dioxide metal complexes have shown powerful catalytic capability in various reactions owing to their tuneable electronic and steric chiral scaffolds.[7,8] Initially, we investigated the *N,N′*-dioxide ligand **L1**, derived from L-proline, complexed with several metal salts to evaluate their ability to promote the asymmetric addition of cyclohexane-1,3-dione (**2a**) to β,γ-unsaturated α-ketoester **1a** in CH_2Cl_2 at room temperature. As shown in Table 1, the rare-metal



complexes promoted the reaction smoothly in 12 h, however the selectivity for the (*S*)-enantiomer was very poor (Table 1, entries 1–3). Other conditions were investigated using rare-metal complexes, however, no better results were obtained. To our delight, Cu(OTf)$_2$ gave the best results and gave **3a** for the (*R*)-enantiomer in 85% yield with 75% *ee* after 12 h (Table 1, entry 4). The ^{1}H and ^{13}C NMR spectra revealed that product **3a** was obtained as an equilibrating mixture of anomers and the cyclic compound was the major product.[9] Encouraged by this result, other reaction parameters were tested. Screening of solvent revealed that the

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[**] OTf = trifluoromethanesulfonate.

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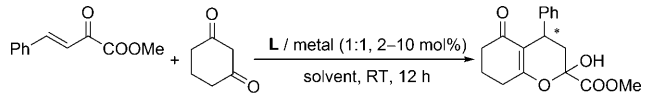
Table 1. Optimization of enantioselective conjugate addition of cyclohexane-1,3-dione (**2a**) to **1a**.[a]



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

Entry	Ligand	Metal	Solvent	Yield [%][b]	*ee* [%][c]
1	**L1**	$La(OTf)_3$	CH_2Cl_2	94	11(*S*)[e]
2	**L1**	$Yb(OTf)_3$	CH_2Cl_2	78	41(*S*)[e]
3	**L1**	$Y(OTf)_3$	CH_2Cl_2	95	31(*S*)[e]
4	**L1**	$Cu(OTf)_2$	CH_2Cl_2	85	75(*R*)[e]
5	**L1**	$Cu(OTf)_2$	PhMe	41	7
6	**L1**	$Cu(OTf)_2$	$CHCl_3$	79	7
7	**L1**	$Cu(OTf)_2$	THF	40	41
8	**L1**	$Cu(OTf)_2$	Et_2O	77	13
9	**L2**	$Cu(OTf)_2$	CH_2Cl_2	99	67
10	**L3**	$Cu(OTf)_2$	CH_2Cl_2	77	49
11	**L4**	$Cu(OTf)_2$	CH_2Cl_2	80	27
12	**L5**	$Cu(OTf)_2$	CH_2Cl_2	71	0
13	**L6**	$Cu(OTf)_2$	CH_2Cl_2	57	0
14	**L7**	$Cu(OTf)_2$	CH_2Cl_2	92	65
15	**L8**	$Cu(OTf)_2$	CH_2Cl_2	90	69
16	**L9**	$Cu(OTf)_2$	CH_2Cl_2	99	99
17[d]	**L9**	$Cu(OTf)_2$	CH_2Cl_2	99	99(*R*)[e]
18[d]	**L9**	–	CH_2Cl_2	no reaction	–
19[d]	–	$Cu(OTf)_2$	CH_2Cl_2	no reaction	–

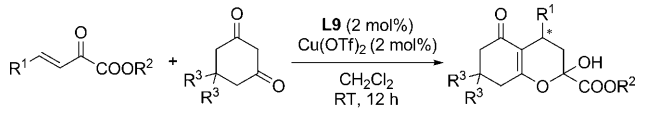
[a] Unless otherwise noted, the reactions were performed with **2a** (0.10 mmol), **1a** (0.12 mmol), *N,N′*-dioxide (0.01 mmol), metal (0.01 mmol) in solvent (1.0 mL) at room temperature for 12 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis. [d] 2 mol% catalyst loading (0.004 mmol **L9** and 0.004 mmol $Cu(OTf)_2$), **1a** (0.2 mmol), **2a** (0.2 mmol) in CH_2Cl_2 (1.0 mL) at room temperature for 12 h. [e] Entries 1–3 *S*, the others *R*, the absolute configuration was determined by comparison to literature data.[6c]

choice of solvent had a pronounced effect on reactivity and enantioselectivity. Other organic solvents including toluene, $CHCl_3$, THF, and Et_2O all showed highly deleterious effects on reactivity and enantioselectivity (less than 41% *ee*, Table 1, entries 5–8).

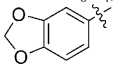
Next we focused on the optimization of the reaction conditions to improve the efficiency of $Cu(OTf)_2$ with other ligands. Various *N,N′*-dioxide ligands with different chiral backbone moieties and amines were investigated. The steric effect of the amide moiety played a crucial role in the enantioselectivity of the reaction. Decreasing the steric hindrance of the amide moiety led to a dramatic decrease in the enantioselectivity (Table 1, entries 9–11).When **L5** and **L6** were used (derived from aniline and benzylamine, respectively), a racemic mixture was obtained (Table 1, entries 12 and 13, respectively). The chiral backbone of the *N,N′*-dioxides also had significant impact on the enantioselectivity. Neither **L7** (derived from L-pipecolic acid) nor **L8** (derived from L-ramipril acid) gave better results than the L-proline-derived **L1** (Table 1, entries 14 and 15). Surprisingly, remarkable improvement on activity and enantioselectivity was achieved by shortening the linkage between the two chiral backbones. Previously, we have found that the *N,N′*-dioxide ligand is optimized by incorporating a three-carbon linkage. However, *N,N′*-dioxide **L9** containing a two-carbon linkage gave **3a** in 99% yield and with 99% *ee* (Table 1, entry 16). To our delight, the catalyst loading could be decreased from 10 to 2 mol% without decreasing the yield or enantioselectivity (Table 1, entry 17). Notably, this process could also tolerate air and moisture. The experimental procedure was very simple, since neither ligand nor metal could promote the reaction, therefore preparing the catalyst beforehand was unnecessary (Table 1, entries 17–19). The experimental procedure was as follows: the substrate, ligand, and metal were weighed in a dry reaction tube followed by addition of CH_2Cl_2 and the reaction mixture was stirred at room temperature for 12 h.

Under the optimized reaction conditions (Table 1, entry 17), the substrate scope for asymmetric conjugate addition of cyclic diketones to various β,γ-unsaturated α-ketoesters was examined and the results are summarized in Table 2. Substrate **1b** with an ethyl group on the ester moiety (R^2) gave a 97% yield with 98% *ee* (Table 2, entry 3). Additionally, dimedone (**2b**) is also a good nucleophile for the reaction, and gave the product in 99% yield with 97% *ee* (Table 2, entry 2). The substrates with electron-withdrawing or donating groups at the *meta*-, *para*-, or *ortho*-position of the aromatic ring were well tolerated in terms of yield and enantioselectivity (up to 99% yield and

Table 2. Substrate scope for catalytic asymmetric conjugate addition of cyclic diketones to β,γ-unsaturated α-ketoesters.[a]



1a, 1c–1r: R^2 = Me; **1b**: R^2 = Et; **2a**: R^3 = H; **2b**: R^3 = Me; **3**

Entry[a]	R^1, R^2	Product	Yield [%][b]	*ee* [%][c]
1	Ph, Me (**1a**)	**3a**	99	99 (*R*)[e]
2	Ph, Me (**1a**)	**3a′**[d]	99	97 (*R*)[e]
3	Ph, Et (**1b**)	**3b**	97	98 (*R*)[e]
4	3-MeC_6H_4, Me (**1c**)	**3c**	99	99
5	4-MeC_6H_4, Me (**1d**)	**3d**	93	99
6	3-$MeOC_6H_4$, Me (**1e**)	**3e**	99	98
7	4-$MeOC_6H_4$, Me (**1f**)	**3f**	91	99
8	 , Me (**1g**)	**3g**	96	99
9	4-PhC_5H_4, Me (**1h**)	**3h**	95	99
10	2-ClC_6H_4, Me (**1i**)	**3i**	96	91
11	3-ClC_6H_4, Me (**1j**)	**3j**	99	99
12	4-ClC_6H_4, Me (**1k**)	**3k**	90	99
13	2,4-$Cl_2C_6H_3$, Me (**1l**)	**3l**	73	93
14	3-BrC_6H_4, Me (**1m**)	**3m**	93	99
15	4-BrC_6H_4, Me (**1n**)	**3n**	87	98
16	4-FC_6H_4, Me (**1o**)	**3o**	99	98
17	2-naphthyl, Me (**1p**)	**3p**	99	99
18	2-thienyl, Me (**1q**)	**3q**	92	98
19	PhCH=CH, Me (**1r**)	**3r**	67	95

[a] Unless otherwise noted, the reactions were performed with **2a** (0.20 mmol), **1** (0.20 mmol), *N,N′*-dioxide **L9** (2 mol%), $Cu(OTf)_2$ (2 mol%) in CH_2Cl_2 (1.0 mL) and the reaction was stirred at room temperature for 12 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis. [d] Dimedone **2b** instead of **2a**. [e] The absolute configuration was determined by comparison to literature data.[6b,c]

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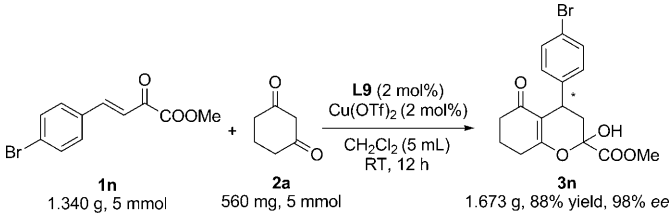
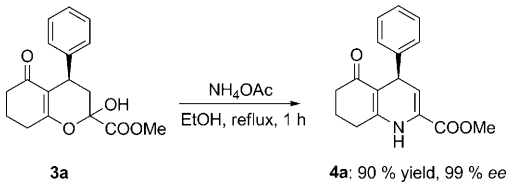
99% *ee*, Table 2, entries 4–16). Notably, the condensed-ring and heteroaromatic alkenes also performed well, to give the corresponding products in excellent yields and enantioselectivities (Table 2, entries 17 and 18). Moreover, the substrate with a cinnamyl group also gave a moderate yield and an excellent *ee* value (Table 2, entry 19). Upon scaling up to gram quantities, the desired product **3a** was still obtained with excellent results (1.673 g, 88% yield, 98% *ee*, Scheme 1) with 2 mol% of the **L9**-$Cu(OTf)_2$ complex.



Scheme 1. Asymmetric Michael reaction on a gram scale.

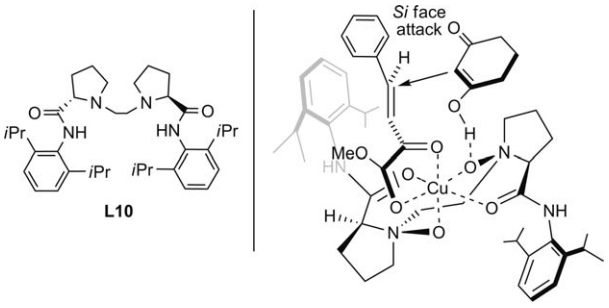
The highly enantiomerically enriched compounds **3** obtained by this method can be easily converted into hexahydroquinoline. Hexahydroquinoline derivatives are important due to their wide applications in medicinal chemistry, including calcium channel activity, bronchodilators, antiatherosclerotics, antidiabetic, and so forth.[10] Hence, the synthesis of hexahydroquinoline derivatives has attracted considerable attention.[11] For example, compound **3a** could be converted to hexahydroquinoline **4a** (Scheme 2) in high yield (90%) and with no loss of enantioselectivity (99% *ee*).[12]



Scheme 2. Conversion of **3a** into hexahydroquinoline **4a**.

To understand the reaction mechanism, a C_2-symmetric amide **L10** (the precursor of the chiral *N,N′*-dioxide **L9)** was synthesized (Scheme 3). No adduct was obtained when **L10**-$Cu(OTf)_2$ was employed as the catalyst, which confirmed that the *N*-oxide plays a key role in this reaction. A possible transition state was postulated based on this result and the absolute configuration of the product. We speculate that *N,N′*-dioxide **L9** and β,γ-unsaturated α-ketoester **1a** coordinate with $Cu(OTf)_2$ to form a complex. Subsequently, the cyclic diketone nucleophile attacks from the *Si* face of the double bond to afford the corresponding product **3a** with excellent enantioselectivity.

In conclusion, we have developed a highly enantioselective conjugate addition of cyclic diketones to β,γ-unsaturated α-ketoesters catalyzed by a chiral *N,N′*-dioxide/$Cu(OTf)_2$ complex. With a low catalyst loading of 2 mol% and mild reaction conditions, a series of synthetically useful chiral bicyclic compounds were obtained with excellent results (up to 99% *ee* and near quantitative yield). Upon scale up, the reaction maintained a good yield and excellent enantioselectivity. The addition product was also easily transformed into hexahydroquinoline. Remarkably, atmospheric oxygen and water did not affect the reaction outcome and the procedure was straightforward. Further application of the catalyst system to other reactions is currently ongoing.



Scheme 3. Proposed transition states.

Experimental Section

General procedure: Dichloromethane (1.0 mL) was added to a mixture of the ligand **L9** (2.4 mg, 0.004 mmol), $Cu(OTf)_2$ (1.4 mg, 0.004 mmol), and β,γ-unsaturated α-ketoester **1a** (38.0 mg, 0.2 mmol) and diketone **2a** (22.4 mg, 0.2 mmol), then stirred at room temperature for 12 h. After the reaction was complete, the mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate: 2:1) to afford the desired product **3a** in 99% yield with 99% *ee*.

Acknowledgements

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Keywords: asymmetric catalysis · copper · hexahydroquinoline · ketoesters · Michael addition

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