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Asymmetric Catalysis

Enantioselective Copper(I/II)-Catalyzed Conjugate Addition of Nitro Esters to β,γ-Unsaturated α-Ketoesters

Sheng Zhang, Kun Xu, Fengfeng Guo, Yanbin Hu, Zhenggen Zha, and Zhiyong Wang*[a]

Abstract: A highly enantioselective Michael addition of nitroacetates to β,γ-unsaturated α-ketoesters was developed by using chiral copper catalysts. The Michael addition products can be obtained in high yields with up to 99% *ee*. With these densely functionalized products, the chiral cyclic nitrones, which are important synthetic intermediates, can be obtained in one step.

The conjugate addition of stabilized carbanions to Michael acceptors represents one of the most useful carbon–carbon bond formation reactions in organic synthesis.[1] The development of chiral catalysts for the asymmetric version of this reaction constitutes an important research field and has been well-explored in recent years.[2] Among various types of Michael donors, nitro esters are active Michael donors with strong acidic α-hydrogen atoms ($pK_a(H_2O) = 9.1$).[3] Additionally, nitro esters can be converted into a number of useful functionalized compounds.[4] Therefore, the asymmetric Michael reactions employing nitroacetates as donors have received increased attention, and most of these reactions utilized organocatalysts.[5] Meanwhile, β,γ-unsaturated α-ketoesters are considered as versatile synthons because of their dense functionalization.[6] In this context, we chose β,γ-unsaturated α-ketoesters as an electrophile in the Michael reaction and realized a highly enantioselective conjugate addition of nitro esters to β,γ-unsaturated α-ketoesters in the presence of chiral copper complexes, affording the desired adducts with excellent enantiomeric excesses and yields. This is an ongoing study of tridentate ligand–metal-complex-catalyzed asymmetric reactions.[7,8]

First of all, the reaction of ethyl nitroacetate **1a** with β,γ-unsaturated α-ketoester **2a** was chosen as a model reaction. A preliminary result of 49% *ee* was obtained. Afterwards, the optimization of various ligands was performed for this reaction (see the Supporting Information for details). To our delight, the chiral ligand **L1**, which was developed for the asymmetric Henry reaction in our group, offered a high enantioselectivity (90% *ee*, Table 1, entry 5).[8] Encouraged by this result, other reaction parameters were varied. Screening of Lewis acids showed that $[Cu(CH_3CN)_4]BF_4$ gave the best result (entries 1–5).

Subsequently, the effects of solvents and ligands on this reaction were examined. Toluene provided the best result among different solvents (Table 1, entries 5–8). Furthermore, the Ar group of the chiral ligand (**L1**–**4**, Table 1) was varied. It was found that **L2** was the most efficient ligand, affording the desired adduct with an excellent enantioselectivity (94% *ee*) and yield (99%) (entry 9). Reaction temperature had a little influence on this reaction. When the reaction temperature decreased from RT to 0 °C, a slightly higher *ee* value was achieved without any loss in the reaction yield. Finally, the optimal reaction conditions were obtained, as shown in entry 9 of Table 1. These conditions were named as conditions I.

Interestingly, when K_2CO_3 was employed instead of Li_2CO_3 as the base, the Cu^I ($[Cu(CH_3CN)_4]BF_4$) could be replaced with Cu^{II} ($Cu(OTf)_2$), affording the addition product with a good result (Supporting Information). Then we optimized the reaction conditions on the basis of this case. Finally, it was found that **L4** was the best ligand and Cs_2CO_3 was the best base for this reaction. Under these conditions the highest reaction yield and an excellent *ee* value were obtained at 0 °C (Table 1, entry 12); these conditions were named as conditions II.

Under the optimized conditions, the substrate scope for asymmetric conjugate addition of nitro esters to various β,γ-unsaturated α-ketoesters was examined and the results were summarized in Table 2. It was found that most reactions with α-keto esters containing γ-aryl or γ-heteroaryl substituents were carried out smoothly in good to excellent yields (80–99%) with excellent enantioselectivities (Table 2, entries 1–14). In terms of Table 2 the steric and electronic properties of substituents on aromatic rings had little effect on the efficiency of this process. Notably, the substrate with a cinnamyl group also gave an excellent *ee* value (Table 2, entry 14). Moreover, γ-alkyl-substituted α-keto esters also performed well to afford the products in good yield with high enantioselectivity (entry 15). Changing the ester groups on nitroacetate (R^1) and ketoesters (R^3) has a little effect on the enantioselectivities and yields (entries 16–21). The reaction of *tert*-butyl nitroacetate was slow at 0 °C (entries 22); However, good yield and enantioselectivity could be obtained when the reactions were performed at 10 °C (entries 16). Upon scaling up to gram quantities, the desired product **3a** was still obtained with excellent results (1.60 g, 91% yield, 94/89% *ee*) as shown in Scheme 1.

[a] *S. Zhang, K. Xu, F. Guo, Y. Hu, Prof. Z. Zha, Prof. Z. Wang*
Hefei National Laboratory for Physical Sciences at Microscale
CAS Key Laboratory of Soft Matter Chemistry
and Department of Chemistry
University of Science and Technology of China
Hefei, Anhui 230026 (China)
Fax:(+86) 551-3603185
E-mail: zwang3@ustc.edu.cn

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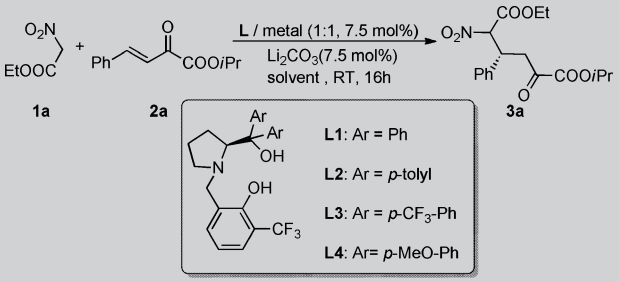
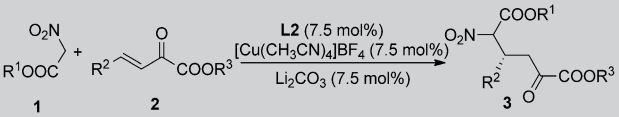
Table 1. Optimization of the reaction conditions.[a]



Entry	Ligand	Metal	Solvent	Yield [%][b]	d.r.[c]	*ee*[d] [%]
1	**L1**	$Cu(OTf)_2$	toluene	81	1:1	63/66
2	**L1**	$Zn(OTf)_2$	toluene	75	1:1	1/5
3	**L1**	$CuBr_2$	toluene	87	1:1	80/89
4	**L1**	$[Cu(CH_3CN)_4]PF_6$	toluene	95	1:1	59/70
5	**L1**	$[Cu(CH_3CN)_4]BF_4$	toluene	99	1:1	90/91
6	**L1**	$[Cu(CH_3CN)_4]BF_4$	CH_2Cl_2	99	1:1	78/86
7	**L1**	$[Cu(CH_3CN)_4]BF_4$	CH_3CN	50	1:1	35/66
8	**L1**	$[Cu(CH_3CN)_4]BF_4$	Et_2O	90	1:1	88/90
9[e]	**L2**	**$[Cu(CH_3CN)_4]BF_4$**	**toluene**	**99 (99)**	**1:1 (1:1)**	**93/94 (94/95)**
10	**L3**	$[Cu(CH_3CN)_4]BF_4$	toluene	89	1:1	84/86
11	**L4**	$[Cu(CH_3CN)_4]BF_4$	toluene	95	1:1	91/93
12[e,f]	**L4**	**$Cu(OTf)_2$**	**toluene**	**99 (99)**	**1:1 (1:1)**	**93/94 (94/95)**

[a] Reactions were carried out with **1a** (0.2 mmol) and **2a** (0.25 mmol) in toluene (2 mL) at room temperature for 16 h, unless otherwise noted. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of products. [d] The *ee* value was determined by chiral HPLC analysis. [e] The data in parentheses is the result of the reaction conducted in 0 °C. [f] Cesium carbonate (7.5 mol%) was used as the base.

Table 2. Conjugate addition of nitroacetates to β,γ-unsaturated α-ketoesters.[a,b]

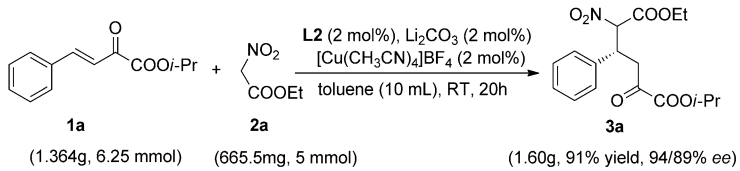


Entry	R^1	R^2	R^3	Product	Yield[c] [%]	d.r[d]	*ee*[e] [%]
1	Et (**1a**)	*i*Pr	Ph (**2a**)	**3a**	99 (99)	1: 1 (1:1)	94/95 (94/95)
2	Et (**1a**)	*i*Pr	4-$NO_2C_6H_5$ (**2b**)	**3b**	99 (99)	1: 1 (1:1)	93/94 (95/97)
3	Et (**1a**)	*i*Pr	4-$CF_3C_6H_5$ (**2c**)	**3c**	99 (98)	1: 1 (1:1)	96/97 (95/97)
4	Et (**1a**)	*i*Pr	4-FC_6H_5 (**2d**)	**3d**	99 (99)	1: 1 (1:1)	95/87 (94/91)
5	Et (**1a**)	*i*Pr	4-ClC_6H_5 (**2e**)	**3e**	99 (99)	1: 1 (1:1)	95/96 (96/91)
6	Et (**1a**)	*i*Pr	4-BrC_6H_5 (**2f**)	**3f**	99 (97)	1: 1 (1:1)	94/97 (95/96)
7	Et (**1a**)	*i*Pr	4-$MeOC_6H_5$ (**2g**)	**3g**	97 (95)	1: 1 (1:1)	93/93 (96/90)
8	Et (**1a**)	*i*Pr	4-MeC_6H_5 (**2h**)	**3h**	97 (99)	1: 1 (1:1)	94/85 (95/93)
9	Et (**1a**)	*i*Pr	3-ClC_6H_5 (**2i**)	**3i**	92 (90)	1: 1 (1:1)	95/95 (92/92)
10	Et (**1a**)	*i*Pr	2-ClC_6H_5 (**2j**)	**3j**	88 (86)	1: 1 (1:1)	92/91 (85/85)
11	Et (**1a**)	*i*Pr	2-naphthyl (**2k**)	**3k**	99 (95)	1: 1 (1:1)	93/95 (91/95)
12	Et (**1a**)	Bn	2-thienyl (**2l**)	**3l**	90 (91)	1: 1 (1:1)	91/95 (96/91)
13	Et (**1a**)	Bn	2-furyl (**2m**)	**3m**	80 (80)	1: 1 (1:1)	96/89 (95/95)
14	Et (**1a**)	*i*Pr	PhCH=CH (**2n**)	**3n**	81 (81)	1: 1 (1:1)	92/91 (91/90)
15	Et (**1a**)	*i*Pr	*n*-pentyl (**2o**)	**3o**	90 (87)	1: 1 (1:1)	92/93 (93/94)
16[f]	*t*Bu (**1b**)	*i*Pr	Ph (**2a**)	**3p**	95 (99)	1: 1 (1:1)	92/92 (95/92)
17	Me (**1c**)	*i*Pr	Ph (**2a**)	**3q**	94 (96)	1: 1 (1:1)	94/93 (89/99)
18	*c*-C_6H_{11} (**1d**)	*i*Pr	Ph (**2a**)	**3r**	92 (94)	1: 1 (1:1)	94/93 (98/99)
19	L-menthyl (**1e**)	*i*Pr	Ph (**2a**)	**3s**	87 (90)	1: 5 (1.5:1)	94/96 (94/99)
20	Et (**1a**)	Me	Ph (**2p**)	**3t**	99 (99)	1: 1 (1:1)	96/90 (94/89)
21	Et (**1a**)	Bn	Ph (**2q**)	**3u**	99 (99)	1: 1 (1:1)	96/95 (99/96)
22	*t*Bu (**1b**)	Me	Ph (**2p**)	**3v**	79 (77)	1: 1 (1:1)	90/91 (89/89)

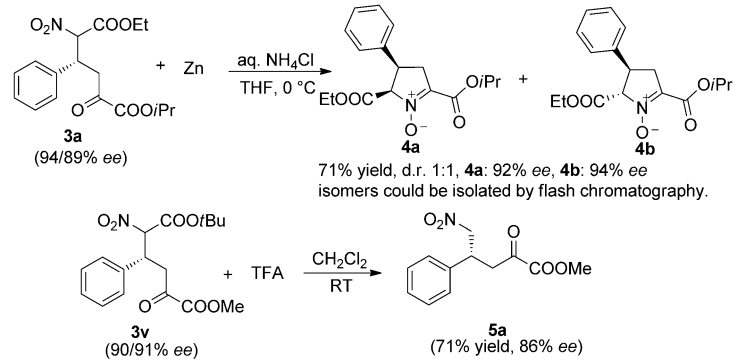
[a] Reactions were carried out with **1a** (0.2 mmol) and **2a** (0.25 mmol), ligand **L2** (7.5 mol%), $Cu[(CH_3CN)_4BF_4]$ (7.5 mol%), Li_2CO_3 (7.5 mol%) in toluene (2 mL) at 0 °C, unless otherwise noted. [b] The data in parentheses is the result of the reaction conducted under condition II. [c] Isolated yield. [d] Determined by ^1H NMR spectroscopic analysis of products. [e] The *ee* value was determined by chiral HPLC analysis. [f] The reaction were performed at 10 °C.

The synthetic utility of this asymmetric transformation was demonstrated by the conversion of adducts into **4a**/**4b**, **5a** as shown in Scheme 2. Chiral cyclic nitrones **4a**/**4b** were prepared from adduct **3a** by a one-step reduction procedure, which could be readily converted to γ-lactam analogues of penicillanic and carbapenicillanic acids.[9] The adduct **3v** underwent a facile acidic hydrolysis to remove an ester group, followed by in situ decarboxylation, affording methyl 5-nitro-2-oxo-4-phenylpentanoate (**5a**) in a moderate yield and with moderate enantioselectivity. To the best of our knowledge, there is no established method to produce 5-nitro-2-oxopentanoates from the direct conjugate addition of nitroalkanes to β,γ-unsaturated α-ketoesters.[10]

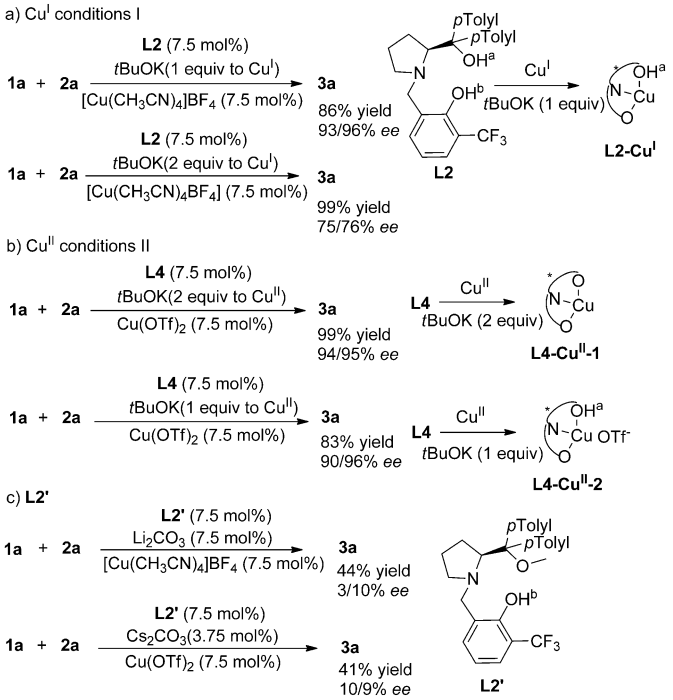
Next, the mechanism of the reaction was studied. We found that similar results were obtained under conditions I and conditions II. A weak base, Li_2CO_3 and Cu^I, was used in conditions I, while a stronger base, Cs_2CO_3 and Cu^{II}, was used in conditions II.[11] To illustrate the role of Li_2CO_3, *t*BuOK was used to replace Li_2CO_3 and the loading was varied. As shown in Scheme 3, when one equivalent of *t*BuOK was employed, almost the same result was obtained as using Li_2CO_3. When the amount of *t*BuOK was increased to two equivalents, a significant decrease in enantioselectivity was observed. As we know, one equivalent of HBF_4 was generated when **L2** coordinated with Cu^I. The HBF_4 generated in situ was consumed by one equivalent of base and the excess of base would lead to a background reaction, which has a negative effect on the enantioselectivity. Therefore, one equivalent of Li_2CO_3 functioned as one equivalent of *t*BuOK in this transformation.



Scheme 1. Asymmetric Michael reaction on a gram scale.



Scheme 2. Synthetic manipulation of the Michael addition products.

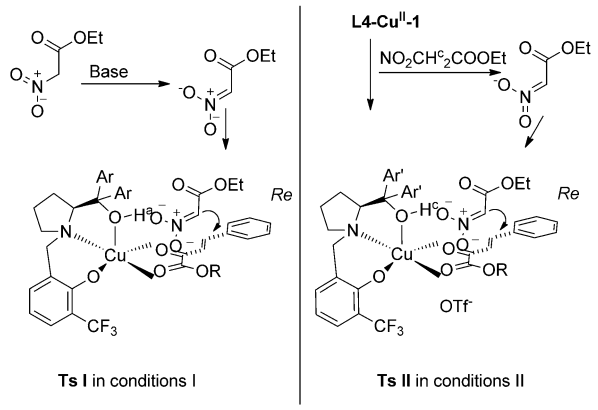


Scheme 3. Control experiments to gain insight into the reaction mechanism.

As for Cs_2CO_3, it was considered as a base which could consume two equivalents of acid to form **L4-Cu^{II}-1**.[8b] The employment of two equivalents of *t*BuOK could afford a similar result as that of one equivalent of Cs_2CO_3, which illustrated the role of Cs_2CO_3, as shown in Scheme 3. The structure of **L4-Cu^{II}-1**, in which the hydrogen of the alcoholic hydroxy group was extracted, was different from **L2-Cu^{I}**. In our previous work, it was found that the oxygen atom of the alcoholic hydroxy group in **L4-Cu^{II}-1**, as a Brønsted base, was able to regain a hydrogen from the nitroalkanes.[8b] Therefore, the reaction could also proceed well with **L4-Cu^{II}-1**. Since the presence of the alcoholic hydroxy group was crucial to the asymmetric Michael addition, we envisioned that the reaction should yield a similar result when one equivalent of *t*BuOK was utilized under conditions II, which was verified by the further experiment.

To further demonstrate the role of the alcoholic hydroxyl group, the ligand **L2′** was synthesized, in which the hydroxyl group was replaced by a methoxy group. In the presence of **L2′**, whether the reaction was under conditions I or II, almost racemic mixtures and low yields were obtained (Scheme 3). Based on these results and the absolute configuration of the product (see the Supporting Information for details), two similar transition-state models (**TS I**/**TS II**), under conditions I and II, were postulated (Scheme 4).[12]

In conclusion, the highly enantioselective copper-catalyzed Michael addition of nitroacetates to β,γ-unsaturated α-ketoesters was developed under mild reaction conditions. A series of versatile chiral adducts were obtained with excellent enantioselectivity and yields. Meanwhile, two transition-state models that attributed to the equal effects of Cu^{I} and Cu^{II} salts on the reaction were proposed. Efforts to apply this catalyst system to other asymmetric transformations are underway in our group.



Scheme 4. Proposed transition-state models for the Michael addition.

Experimental Section

General procedure (conditions I)

A mixture of $[Cu(CH_3CN)_4]BF_4$ (4.7 mg, 0.015 mmol) and the ligand (**L2**, 6.8 mg, 0.015 mmol) in toluene (2 mL) with Li_2CO_3 (1.1 mg, 0.015 mmol) was stirred at room temperature for 1 h under nitrogen. Nitroacetate **1a** (22 μL, 0.2 mmol) was then added and the resulting mixture cooled to 0 °C. After stirring the mixture for 1 h, the β,γ-unsaturated α-ketoester **2a** (55 mg, 0.25 mmol) was added in one portion. After the reaction was complete (monitored by TLC analysis), the reaction was quenched by HCl (2 mL, 2 M) and then

extracted with ethyl acetate (3×2 mL). The organic phase was washed with saturated $NaHCO_3$ and brine, dried with Na_2SO_4, and evaporated in vacuo. Purification of the residue by column chromatography afforded the desired Michael product **3 a** (70 mg), as a light-yellow oil, in 99% yield with 94/95% *ee*. (Chiralcel AD-H+AS-H, *i*PrOH/hexanes = 10:90, 0.5 mL min^{-1}, λ = 215 nm: t_R = 47.4 min (major), t_R = 53.8 min (minor); t_R = 59 min (major), t_R = 50 min (minor)).

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

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[11] The concentration of Cu^{I} did not change from the beginning to the end of the reaction, which showed the complex of Cu^{I} was stabilized under the reaction conditions (see the Supporting Information).

[12] The kinetic study and deuterium-labeling experiment of the reaction under conditions I and II were performed, which could illustrate the difference between the structure of **L2-Cu^{I}** and **L4-Cu^{II}-1** indirectly (see the Supporting Information).

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