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Organocatalytic enantioselective Michael addition of a kojic acid derivative to nitro olefins†

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By employing a chiral bifunctional thiourea–tertiary amine as catalyst, enantioselective Michael addition of a kojic acid derivative to nitro olefins was realised. The reactions afforded the products with good yields (up to 99%) in good enantioselectivities (up to 97% ee). In addition, the absolute configuration of one product was determined.

Introduction

The nitro olefins are important building blocks and intermediates in organic synthesis because the nitro group can be easily transformed into other useful groups such as amines and carbonyls.[1] Asymmetric Michael addition of nitro olefins represents one of the most versatile entries to enantioenriched nitroalkanes. As a result, many efforts have been devoted to the development of this process.[2] Impressive progress has been made with both chiral metal[3] and organocatalysts.[4] Notably, in recent years, many chiral organocatalysts have been successfully employed to promote asymmetric Michael addition of various nucleophiles such as 1,3-dicarbonyl compounds,[5] aldehydes or ketones,[6] oxindoles,[7] arenes,[8] hetero nucleophiles[9] and other nucleophiles[10] to nitro olefins to provide a wide variety of enantioenriched nitroalkanes. While the organocatalytic asymmetric Michael addition of nitro olefins has been explored intensively, we noted that the asymmetric Michael addition of kojic acid to nitro olefins has not been developed yet.

Kojic acid is a natural fungal metabolite. Owing to the diverse biological activities of many kojic acid derivatives, such as chelating activity and inhibition of tyrosinase, a large number of kojic acid derivatives have been prepared for biological evaluation.[11] Kojic acid derivatives were also employed in construction of various biomedicinally important natural products and analogues.[12] However, only a few examples of organocatalyzed asymmetric reactions of kojic acid and its derivatives have been reported.[13] Owing to the good nucleophilicity of kojic acid, we envisioned that chiral bifunctional organocatalysts **1** would catalyze enantioselective Michael addition of a kojic acid derivative (for example, 2-((*tert*-butyldimethylsilyloxy)methyl)-5-hydroxy-4*H*-pyran-4-one **2**[14]) to nitro olefin **3** as outlined in Scheme 1. This transformation would be important because a novel sort of enantioenriched kojic acid derivatives could be obtained. In addition, the corresponding product **4** could undergo oxidative fragmentation to generate β-nitro acid **5**. Following reduction of the nitro group would accomplish the synthesis of enantioenriched β^2-amino acid **6**. β^2-Amino acids are important components in β-peptides.[15] In contrast to β^3-homo-amino acids, β^2-amino acids cannot be obtained simply by homologation of the (natural) α-amino acids, but have to be synthesized by enantioselective reactions. Therefore, synthesis of β^2-amino acids has attracted increasing attention[16,17] and development of a facile strategy for preparation of enantioenriched β^2-amino acids is of great importance.

Herein we present the enantioselective Michael addition of a kojic acid derivative to a wide variety of nitro olefins promoted by bifunctional chiral thiourea–tertiary amine organocatalysts. The reactions proceeded smoothly to provide the desired products in good yields (up to 99%) and good enantioselectivities (up to 97% ee). Subsequent oxidative fragmentation of one of the product afforded the corresponding β-nitro acid. Hence this transformation enables easy access to enantioenriched β^2-amino acids.

Results and discussion

First, 2-((*tert*-butyldimethylsilyloxy)methyl)-5-hydroxy-4*H*-pyran-4-one **2**[14] was selected as the standard substrate in the reaction due to its good solubility. A range of bifunctional thiourea–tertiary amine organocatalysts (Fig. 1) were screened in the Michael addition of **2** to nitro olefin **3a** in toluene at 20 °C for 2 days. The results are summarized in Table 1.

As can be seen in Table 1, all of the catalysts **1a–1j** (Fig. 1) catalyzed the reaction to provide the adduct **4a** in moderate yields. Cinchona alkaloids derived thiourea–tertiary amine catalysts **1a–1d** afforded low enantioselectivities (Table 1, entries 1–4). (1*R*,2*R*)-1,2-Diphenyl-1,2-diamine derived catalyst **1e** also resulted in very low enantioselectivity (Table 1, entry 5). Better

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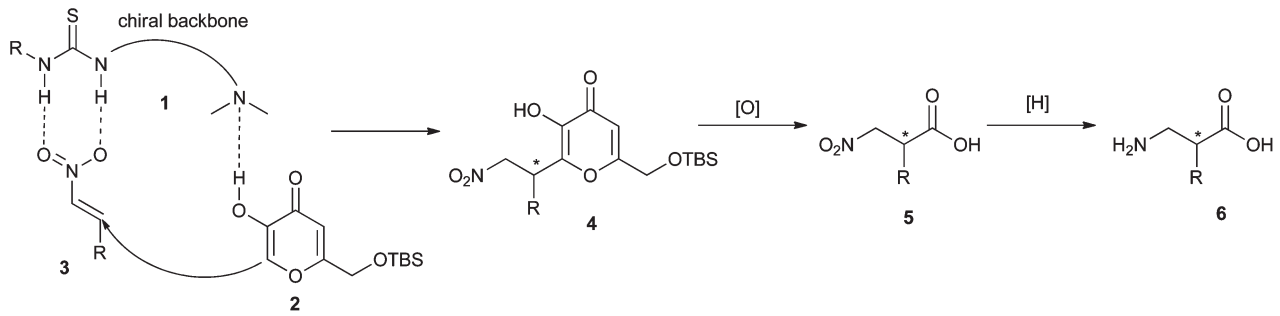


Scheme 1 Proposed chiral bifunctional thiourea–tertiary amine **1** catalyzed Michael addition of kojic acid derivative **2** to nitro olefin **3** and subsequent conversion to enantioenriched β^2-amino acid **6**.

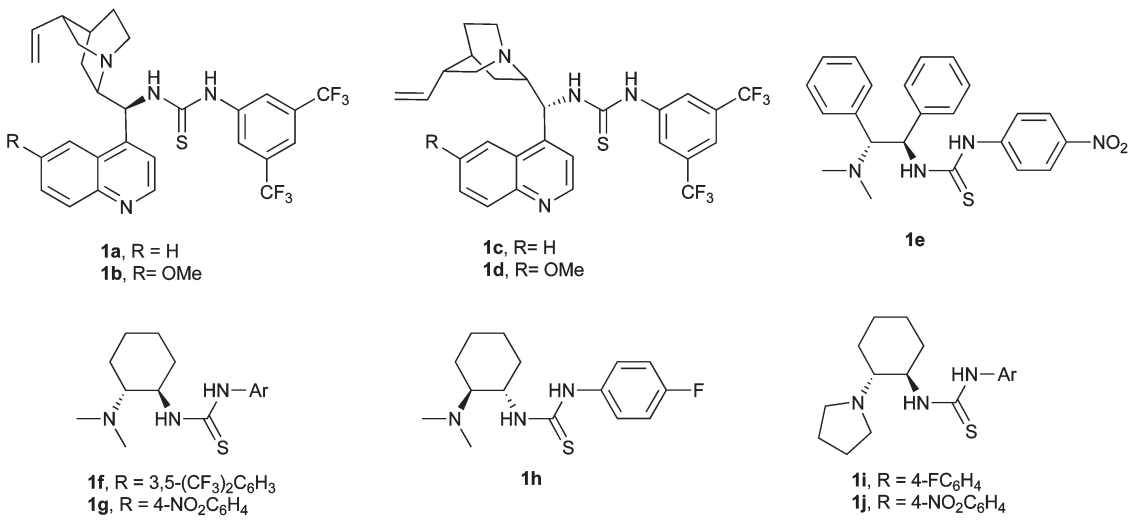


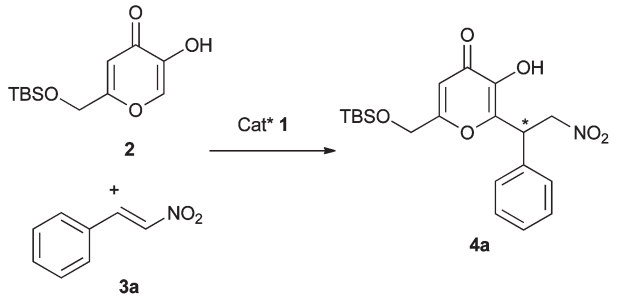
Fig. 1 Chiral bifunctional thiourea–tertiary amine organocatalysts evaluated in this study.

results were observed with *trans*-cyclohexane-1,2-diamine derived thiourea–tertiary amine catalysts **1f–1j** (Table 1, entries 6–10), in which **1j** provided the highest ee value (Table 1, entry 10).

Therefore, **1j** was determined to be the optimal catalyst and was employed in further investigations. Subsequently, various solvents were evaluated. Several aromatic solvents other than toluene delivered very poor yields and ee values (Table 1, entries 11–14). Particularly, no product was obtained in mesitylene, perhaps due to the poor solubility of compound **2** in mesitylene (Table 1, entry 14). Dichloromethane and chloroform also gave only moderate yields and poor ee values (Table 1, entries 15 and 16). Ether led to even lower yield as well as poor enantioselectivity (Table 1, entry 17). Gratifyingly, we found that methanol provided the product in much higher yields with good ee value (Table 1, entry 18), which suggested that alcoholic solvents would benefit the reaction. Consequently several other alcoholic solvents were also tested. However they did not result in better results (Table 1, entries 19–21). Hence methanol was determined as the most favourable solvent to the reaction. Addition of 4 Å molecular sieve led to erosion both in yield and ee value (Table 1, entry 22). Enhancing the catalyst loading to 15 mol% did not improve the enantioselectivity (Table 1, entry 23). Afterwards the temperature was also investigated. Lowering the temperature to 0 °C caused no change in ee value (Table 1, entry 24). To our delight, when the reaction was conducted at −10 °C for 4 days, the product was obtained in excellent yield with good enantioselectivity (Table 1, entry 25). Further lowering the temperature to −20 °C resulted in decrease in ee value (Table 1, entry 26).

Having established the optimal conditions, the enantioselective Michael addition was expanded to a wide variety of nitro olefins. The results are summarized in Table 2. Generally, the reaction of aromatic nitro olefins bearing electron-withdrawing substituents in the *para* position of the phenyl groups with kojic acid derivative **2** proceeded smoothly to provide the corresponding products in good enantioselectivities (Table 2, entries 2–5). Meanwhile, electron-donating substituents in the *para* position of the phenyl groups caused slightly decrease in ee values (Table 2, entries 6 and 7). Aromatic nitro olefins bearing substituents in the *ortho* position or the *meta* position of the phenyl groups also afforded the corresponding products in inferior enantioselectivities (Table 2, entries 8–12). However, 1-naphthyl nitro olefin **3m** exhibited good enantioselectivity (Table 2, entry 13). By employing 20 mol% of catalyst **1j**, the highest ee value of 97% ee was obtained with heteroaryl nitro olefin **3n**, although

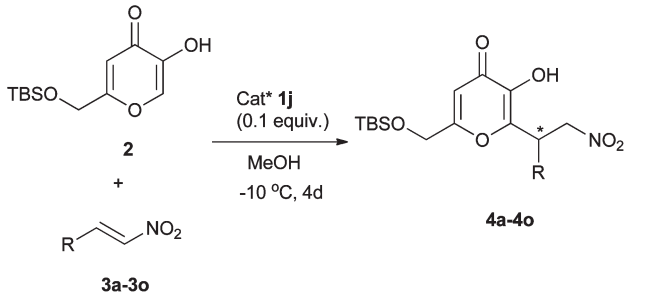
Table 1 Enantioselective Michael addition of kojic acid derivative **2** to nitro olefin **3a**[a]



Entry	Cat*	Solvent	*T* (°C)	Yield[b] (%)	ee[c] (%)
1	**1a**	Toluene	20	69	−31
2	**1b**	Toluene	20	65	−35
3	**1c**	Toluene	20	71	30
4	**1d**	Toluene	20	68	40
5	**1e**	Toluene	20	54	29
6	**1f**	Toluene	20	84	48
7	**1g**	Toluene	20	64	52
8	**1h**	Toluene	20	84	−70
9	**1i**	Toluene	20	80	77
10	**1j**	Toluene	20	82	79
11	**1j**	Xylene	20	57	56
12	**1j**	Mesitylene	20	NR	—
13	**1j**	C_6H_5Cl	20	59	45
14	**1j**	$C_6H_5CF_3$	20	59	48
15	**1j**	CH_2Cl_2	20	59	46
16	**1j**	$CHCl_3$	20	69	54
17	**1j**	Et_2O	20	20	42
18	**1j**	MeOH	20	95	83
19	**1j**	EtOH	20	75	81
20	**1j**	i-PrOH	20	95	81
21	**1j**	$HOCH_2CH_2OH$	20	27	45
22[d]	**1j**	MeOH	20	74	71
23[e]	**1j**	MeOH	20	87	80
24[f]	**1j**	MeOH	0	82	82
25[g]	**1j**	MeOH	−10	95	90
26[h]	**1j**	MeOH	−20	81	85

[a] Unless specified otherwise, reactions were carried out with **2** (0.15 mmol), **3a** (0.1 mmol) and the catalyst in the solvent (3 mL) at 20 °C for 2 days. [b] Isolated yield based on **3a**. [c] The ee values were determined by using chiral HPLC. [d] With 4 Å MS as additive. [e] 15 mol % of **1j** was used. [f] The reaction was carried at 0 °C for 3 days. [g] The reaction was carried at −10 °C for 4 days. [h] The reaction was carried at −20 °C for 6 days.

Table 2 Enantioselective Michael addition of kojic acid derivative **2** to nitro olefins **3a–3o**[a]



Entry	**3** (R)	Yield[b] (%)	ee[c] (%)	Conf.[d]
1	**3a** (Ph)	95	90	*R* (+)
2	**3b** (4-FC_6H_4)	85	92	(+)
3	**3c** (4-ClC_6H_4)	86	93	(+)
4	**3d** (4-BrC_6H_4)	83	94	(+)
5	**3e** (4-$O_2NC_6H_4$)	84	89	(+)
6	**3f** (4-MeC_6H_4)	77	87	(+)
7	**3g** (4-$MeOC_6H_4$)	80	88	(+)
8	**3h** (2-ClC_6H_4)	99	81	(+)
9	**3i** (2,4-$Cl_2C_6H_3$)	92	83	(+)
10	**3j** (2-BrC_6H_4)	87	83	(+)
11	**3k** (2-$O_2NC_6H_4$)	80	86	(+)
12	**3l** (3-BrC_6H_4)	89	87	(+)
13	**3m** (1-Naphthyl)	86	91	(+)
14[e]	**3n** (2-Thienyl)	58	97	(+)
15[f]	**3o** (c-C_6H_{11})	68	89	(+)

[a] Unless specified otherwise, reactions were carried out with **2** (0.15 mmol), **3** (0.1 mmol), and the catalyst **1j** (10 mol%) in methanol (3 mL) at −10 °C for 4 days. [b] Isolated yield based on **3**. [c] The ee values were determined by using chiral HPLC. [d] The absolute configuration of **4a** was determined by comparison of the optical rotation value with the literature datum after being converted into a known compound.[17b,18a,b] [e] 20 mol% of **1j** was employed. [f] The ee value was determined by using HPLC after **4o** was deprotected.

in poor yield (Table 2, entry 14). Furthermore, cyclohexyl nitro olefin **3o** was also subjected to the reaction and gave the product with good enantioselectivity in moderate yield (Table 2, entry 15).

To illustrate the synthetic utility of this methodology and further confirm the absolute stereochemistry of this reaction, the product **4a** was subjected to oxidative fragmentation[18] to give β-nitro acid **5a**. Subsequent esterification of **5a** afforded ester **7** which is a known compound.[17b,18a,b] By comparison of the optical rotation value of **7** with the literature datum, the configuration was determined as *R*. Notably, enantioenriched β^2-amino acid **6a** can be easily prepared from β-nitro acid **5a** *via* hydrogenation according to the literature.[17b] Thus a valuable strategy for the synthesis of enantioenriched β^2-amino acids has been well established (Scheme 2).

Conclusions

In conclusion, we have developed an efficient enantioselective bifunctional chiral thiourea–tertiary amine catalyzed Michael addition of a kojic acid derivative to nitro olefins. The reactions proceeded smoothly to provide the corresponding products with good yields (up to 99%) in good enantioselectivities (up to 97%). By oxidative fragmentation and following esterification, product **4a** was readily converted into known β-nitro ester **7**. The absolute configuration of **4a** was determined as *R* by comparison of the optical rotation value of **7** with the literature datum. This transformation also provided a facile way to synthesize enantioenriched β^2-amino acids. Further investigations of the scope and synthetic utility of this chemistry are under way.

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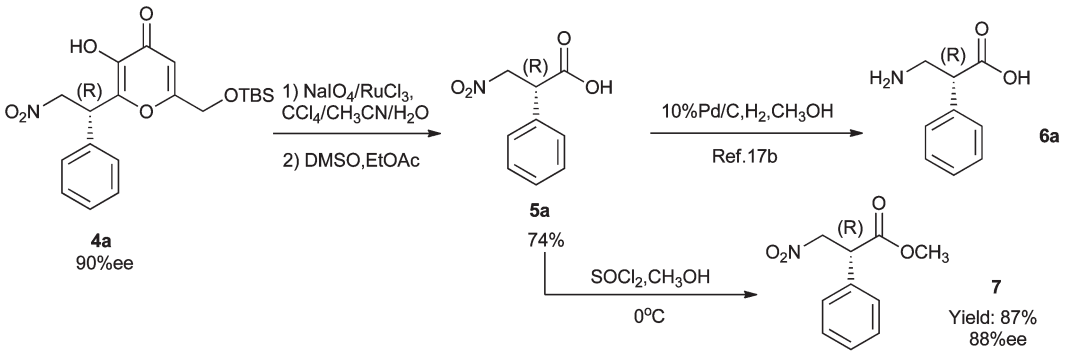

Scheme 2 Oxidative fragmentation of the product **4a** and determination of the absolute configuration.

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