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Enantioselective 1,4-addition of kojic acid derivatives to β-nitroolefins catalyzed by a cinchonine derived sugar thiourea†

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A highly enantioselective Michael addition reaction of kojic acid derivatives to β-nitroolefins has been accomplished using a cinchonine derived sugar thiourea. The reaction provides the corresponding Michael adducts in excellent yields with a high degree of enantioselectivity (up to 99% ee) in short reaction time with low catalyst loading. The Michael adducts are found to exhibit promising cytotoxicity against various cancer cell lines.

Introduction

The Michael addition is one of the most elegant approaches for the construction of carbon\carbon bonds under mild conditions in an atom economic fashion.[1] In particular, asymmetric Michael reaction[2] of nitroalkenes is very attractive to produce the enantiopure nitroalkanes which are important building blocks for the synthesis of chiral amines.[3] Recently, cinchona derived thiourea catalysts have received special attention in the field of organocatalysis.[4] Among them, sugar–cinchona hybrid thiourea catalysts[5] have proved to be highly efficient for the enantioselective Michael reaction.

Kojic acid is a fungal metabolite and is known to exhibit a broad spectrum of biological activities such as antimicrobial,[6] cosmetics,[7] pesticide/insecticide,[8] antitumor,[9] antidiabetic,[10] and anticonvulsant activity.[11] Consequently, a large number of kojic acid derivatives have been prepared to evaluate their efficiency in biological systems.[12] In addition, kojic acid has also been used for the synthesis of biologically active natural products.[13] In fact, kojic acid acts as a highly reactive nucleophile in 1,4-addition reactions.[14] On the other hand, asymmetric Michael addition of kojic acid derivatives to nitroalkenes provides a direct access to enantiomerically enriched nitro compounds[15] which are key intermediates for β-peptides.[16]

Inspired by recent advancements in thiourea catalysis we herein report the asymmetric Michael addition of kojic acid derivatives to β-nitrostyrenes to produce the Michael adducts in high yields with good to excellent enantioselectivity using a novel series of cinchona derived sugar thiourea catalysts.

Initially, we investigated the catalytic efficiency of thiourea catalysts **I–XII** (Fig. 1) was evaluated in the Michael addition of kojic acid TBS ether (**1**) to β-nitrostyrene (**2a**). Remarkably, the reaction proceeds at low concentration of the catalyst **II** with enhanced reaction rates compared to previously reported catalysts.[15]

Cinchona thioureas (**I–XII**) containing different chiral diamine skeletons were chosen as the catalysts (Fig. 1). Accordingly, treatment of kojic acid TBS ether (**1**) with β-nitrostyrene (**2a**) in the presence of catalysts **I** and **VII** in CH_2Cl_2 at 30 °C afforded the desired product **3a** reasonably in good yield with moderate ee (Table 1, entries a and s). Replacement of the catalyst **I** and **VII** with **IV** and **X** gave the product **3a** in low ee with opposite asymmetric induction (Table 1, entries p and v). The above reaction was further carried out with other catalysts **II**, **V**, **VIII** and **XI** to evaluate their efficiency. But to our surprise, the catalysts **II** and **VIII** gave the Michael adduct **3a** in excellent yields (85 and 80%) with good ee 75 and 71% respectively (Table 1, entries b and t).

However, the catalysts **V** and **XI** gave the product **3a** in similar yields but with low ee (Table 1, entries q and w). The efficiency of other cinchona bifunctional thiourea catalysts such as **III**, **VI**, **IX** and **XII** was also tested in the above reaction. None of them gave the **3a** with satisfactory yields and enantioselectivity (Table 1, entries o, r, u and x).

After numerous experiments, the catalyst **II** was found to be superior in terms of yield and enantioselectivity (75% ee, Table 1, entry b) than other catalysts. With the best catalyst in hand, we next screened the effect of other parameters like solvent, temperature and catalyst loading. Of various solvents tested, the

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† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectrum of products. Detailed procedures and spectroscopic data for novel catalysts. Copies of ^{1}H NMR, ^{13}C NMR and HPLC data of novel compounds and catalysts prepared are available. See DOI: 10.1039/c3ra47423b

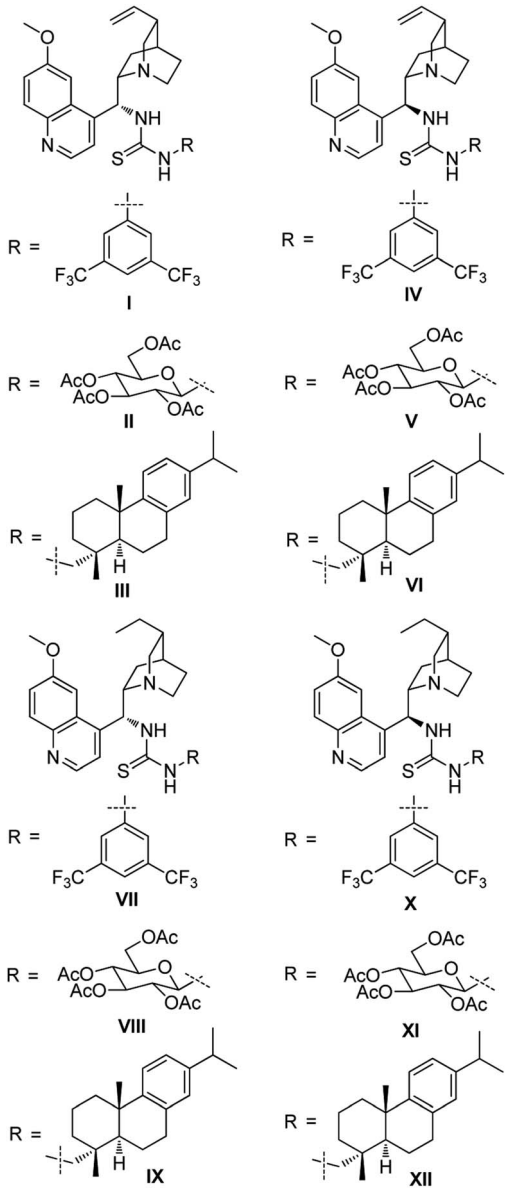
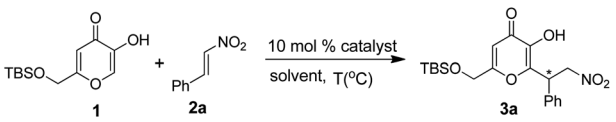


Fig. 1 Representative bifunctional thiourea catalysts.

Table 1 Screening of thiourea catalysts in the Michael reaction of kojic acid TBS ether (**1**) with β-nitrostyrene (**2a**)



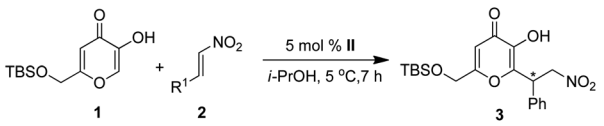
Entry	Catalyst[a]	Solvent	T (°C)	Yield (%)[b]	ee (%)[c]
a	**I**	CH_2Cl_2	30	75	68
b	**II**	CH_2Cl_2	30	85	75
c	**II**	$PhCH_3$	30	89	78
d	**II**	Xylene	30	90	85
e	**II**	CH_3CN	30	91	79
f	**II**	EtOH	30	94	85
g	**II**	THF	30	93	78
h	**II**	MeOH	30	96	89
i	**II**	Et_2O	30	71	67
j	**II**	i-PrOH	30	97	91
k	**II**	i-PrOH	−10	96	97
l	**II**	i-PrOH	0	97	98
m	**II**	i-PrOH	5	98	99
n	**II**	i-PrOH	5	98	99[d]
o	**III**	CH_2Cl_2	30	71	55
p	**IV**	CH_2Cl_2	30	74	−56
q	**V**	CH_2Cl_2	30	84	−55
r	**VI**	CH_2Cl_2	30	76	−45
s	**VII**	CH_2Cl_2	30	76	67
t	**VIII**	CH_2Cl_2	30	80	71
u	**IX**	CH_2Cl_2	30	78	54
v	**X**	CH_2Cl_2	30	72	−52
w	**XI**	CH_2Cl_2	30	79	−56
x	**XII**	CH_2Cl_2	30	76	−54

[a] Reaction was carried out with **1** (0.2 mmol), **2a** (0.22 mmol) in the presence of 10 mol% of organocatalyst. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 5 mol% catalyst used.

best results were achieved in *i*-PrOH, whereas the moderate enantioselectivity was observed in xylene, EtOH and MeOH. However, poor yields and low enantioselectivity were obtained in toluene, CH_3CN, THF and Et_2O. Therefore, *i*-PrOH was chosen as the optimal solvent for this reaction (91% ee). Indeed, the temperature was found to have a significant influence on the enantioselectivity. For example, lowering the reaction temperature to −10 °C, the product **3a** was obtained in 96% yield with 97% ee (Table 1, entry k) after a long reaction time. By increasing the reaction temperature to 5 °C, the reaction was complete in short time with a gradual increase of yield and ee (Table 1, entry l and m). By decreasing the amount of the catalyst from 10 to 5 mol% did not alter the yield and enantioselectivity (98% of yield and 99% of ee, Table 1, entry n). Therefore, no significant effect of the catalyst loading either on yield or enantioselectivity was observed. Thus, the optimal reaction conditions for the Michael addition were determined to be 0.1 mmol of the kojic acid TBS ether (**1**), 0.11 mmol of β-nitrostyrene (**2a**), 5 mol% of the catalyst **II** in 1 mL *i*-PrOH at 5 °C for 7 h. The scope of the reaction was further investigated under optimized conditions and the results are summarized in Table 2. Notably, several aromatic nitroalkenes afforded the desired products in high to excellent enantioselectivities (Table 2, 90–99%, entries a–s) with (*R*)-configuration. The absolute configuration of the Michael products was assigned by comparison of the optical rotation with known compounds.[15] It was found that nitroolefins (**2**) either with electron-withdrawing or with electron-donating groups on the phenyl ring gave the products in good to excellent yields (85–99%) with high enantioselectivity (84–99% ee). In addition, heteroaromatic substrates such as 2-furanyl and 2-thienyl gave the Michael adducts with good yields and ee (Table 2, entries r and s). It is noteworthy to mention that aliphatic nitroalkene also furnished the Michael adduct with excellent selectivity (Table 2, entry t, 89% ee). A large number of kojic acid derivatives (**3a–3t**) were prepared in high yields with excellent enantioselectivities (up to 99% ee).

Encouraged by the above results, we turned our attention to evaluate the synthetic potential of catalyst **II** in Michael reaction

Table 2 Michael reaction of kojic acid TBS ether (**1**) with various nitroolefins



1 2 3

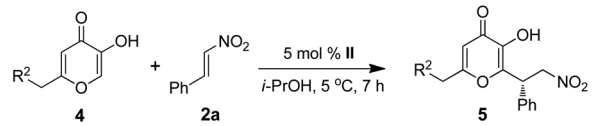
Entry	R^1	Product[a]	Yield (%)[b]	ee (%)[c]	Conf.
a	C_6H_5	**3a**	97	99	*R*
b	4-FC_6H_4	**3b**	98	96	*R*
c	4-ClC_6H_4	**3c**	97	94	*R*
d	4-BrC_6H_4	**3d**	95	94	*R*
e	4-MeC_6H_4	**3e**	90	91	*R*
f	4-$MeOC_6H_4$	**3f**	95	91	*R*
g	3-FC_6H_4	**3g**	96	85	*R*
h	3-ClC_6H_4	**3h**	95	88	*R*
i	2-FC_6H_4	**3i**	99	95	*R*
j	2-ClC_6H_4	**3j**	98	88	*R*
k	2-BrC_6H_4	**3k**	96	91	*R*
l	2-$MeOC_6H_4$	**3l**	97	88	*R*
m	2-Naphthyl	**3m**	93	91	*R*
n	2-$BnOC_6H_4$	**3n**	92	84	*R*
o	2,4-$Cl_2C_6H_3$	**3o**	95	87	*R*
p	3,4-$Cl_2C_6H_3$	**3p**	94	91	*R*
q	3,5-$(Me)_2C_6H_3$	**3q**	90	95	*R*
r	2-Furanyl	**3r**	94	95	*R*
s	2-Thienyl	**3s**	85	92	*R*
t	Butyl	**3t**	90	89	*S*

[a] Reaction was carried out with **1** (0.1 mmol), **2** (0.11 mmol), and in 1 mL of *i*-PrOH. [b] Isolated yields. [c] Determined by chiral HPLC.

of **4a** and **4b** to β-nitrostyrene **2a**. Interestingly, the reaction proceeded effectively under present conditions to afford the respective Michael products **5a** and **5b** in good yields (96–95%) with excellent enantioselectivity (95–97%) (Table 3, entries a and b).

Based on the above results, a possible ternary complex of the catalyst **II** was proposed in Fig. 2. According to the results reported in Table 2, it was believed that nitroolefin could be effectively activated by thiourea moiety of the catalyst, while the tertiary amine deprotonates the enolic OH to generate the kojic acid enolate. In a ternary complex, both nitroolefin and kojic acid coordinate with thiourea, tertiary amine and

Table 3 Enantioselective Michael addtion of kojic acid derivatives (**4a** and **b**) to β-nitrostyrene (**2a**)



4 2a 5

Entry	R^2	Product[a]	Yield (%)[b]	ee (%)[c]	Conf.
a	H	**5a**	96	95	*R*
b	4-ClC_6H_4S–	**5b**	95	97	*R*

[a] Reaction was carried out with **1** (0.1 mmol), **2** (0.11 mmol), and in 1 mL of *i*-PrOH. [b] Isolated yields. [c] Determined by chiral HPLC.

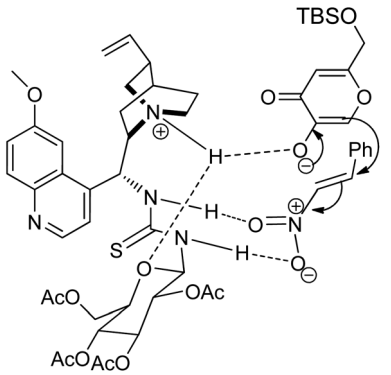


Fig. 2 A plausible ternary complex.

carbohydrate of the catalyst **II** respectively through hydrogen bonding. The nucleophilic attack of the enolate on β-nitrostyrene from the *Re*-face leading to the formation of (*R*)-enantiomer as a major product, which is consistent with the observed results. The attack of enolate to the *Si*-face of the nitroolefin is restricted by cinchonine and carbohydrate moieties of the catalyst. The carbohydrate serves as the chiral auxiliary to enhance the selectivity. As shown in Fig. 2, the complexation of cinchonine, thiourea and carbohydrate moieties of the bifunctional catalyst with kojic acid and nitroolefin plays a significant role in controlling the enantioselectivity of the Michael reaction.

Table 4 Anti-proliferative activity (IC_{50}values μM[b]) of Michael adducts on HeLa, A549, DU145, MCF7

Compound[a]	HeLa	A549	DU145	MCF7
3a	53 ± 2.1	38 ± 2.1	31 ± 1.7	60 ± 2.4
3b	>100	47 ± 1.5	40 ± 2.6	56 ± 2.8
3c (racemic)	37 ± 2.3	38 ± 2.7	51 ± 2.9	34 ± 2.4
3c	11 ± 1.5	18 ± 1.7	16 ± 0.8	18 ± 1.1
3d	9.2 ± 1.1	8.3 ± 1.1	13 ± 1.4	24 ± 1.6
3e	15 ± 1.2	29 ± 1.8	51 ± 2.7	53 ± 2.8
3f	27 ± 1.7	38 ± 2.7	>100	>100
3g	34 ± 1.8	84 ± 3.4	36 ± 1.9	44 ± 2.5
3h	10 ± 0.9	9.1 ± 0.8	14 ± 1.2	35 ± 2.4
3i	51 ± 2.6	37 ± 2.8	>100	>100
3j	92 ± 3.3	36 ± 2.4	34 ± 2.6	48 ± 2.4
3k	31 ± 2.8	50 ± 2.8	63 ± 2.7	35 ± 2.1
3l	22 ± 2.1	55 ± 2.7	38 ± 2.8	57 ± 2.6
3m	56 ± 2.4	>100	45 ± 2.6	47 ± 2.6
3n	75 ± 2.9	37 ± 2.4	33 ± 2.4	38 ± 2.8
3o	63 ± 3.7	32 ± 1.9	>100	54 ± 2.4
3p	33 ± 2.5	>100	3.5 ± 1.8	37 ± 1.9
3q	24 ± 1.7	78 ± 2.8	33 ± 2.2	26 ± 1.4
3r	27 ± 1.8	40 ± 2.8	46 ± 2.1	58 ± 2.7
3s	58 ± 3.1	>100	37 ± 2.8	87 ± 2.8
3t	82 ± 2.9	43 ± 1.8	24 ± 2.1	65 ± 3.2
5a	28 ± 2.3	>100	41 ± 2.6	47 ± 1.6
5b	22 ± 1.1	55 ± 2.8	36 ± 2.7	>100

[a] Cell lines were treated with different concentration of compounds for 48 h as described in experimental section. [b] IC_{50} values are indicated as a mean value of three independent experiments.

In vitro anticancer activity

The Michael adducts were evaluated for their anti-proliferative activity against four different human tumor cell lines; HeLa (human epithelial cervical cancer), A549 (human lung carcinoma epithelial), DU145 (human prostate carcinoma epithelial), and MCF-7 (human breast adenocarcinoma). The inhibitory concentration (IC_{50}) values are summarized in Table 4.

As evident from Table 4, the test compounds showed moderate to good cytotoxicity against four different cancer cell lines. The chiral compound **3c** was highly active than its racemic form. The study of % viability *vs* concentration of chiral and racemic products of **3c** is shown in Fig. 3. Compound **3c** was active against A549, DU145, MCF7 cell lines at 18 μM, 16 μM, and 18 μM respectively whereas **3c** was active against HeLa cell lines at 11 μM. Furthermore, compound **3d** showed good activity against HeLa, A549 and DU145 cell lines at 9 μM, 8 μM, and 13 μM respectively while compound **3h** was also active against A549, HeLa and Du145 cell lines at 9 μM, 10 μM and 14 μM respectively.

Conclusion

In conclusion, a novel bifunctional cinchona–sugar based thiourea catalyst has proved to be a highly efficient organocatalyst for the asymmetric Michael addition of kojic acid derivatives to β-nitroolefins. Our approach has significantly improved the reaction rate to 7 h using a new quinine–sugar–thiourea catalyst, whereas the reported reaction took four days for the completion using cyclohexane-derived thiourea catalyst. High enantioselectivity (99%), low catalyst loading (5 mol%), excellent yields, short reaction times, broad substrate scope and mild reaction conditions are the salient features of this methodology. This is the first report on the evaluation of anti-cancer properties of the Michael adducts, which are found to exhibit promising anti-cancer activity. Further application of sugar thiourea catalysts for asymmetric synthesis is under progress in our laboratory.

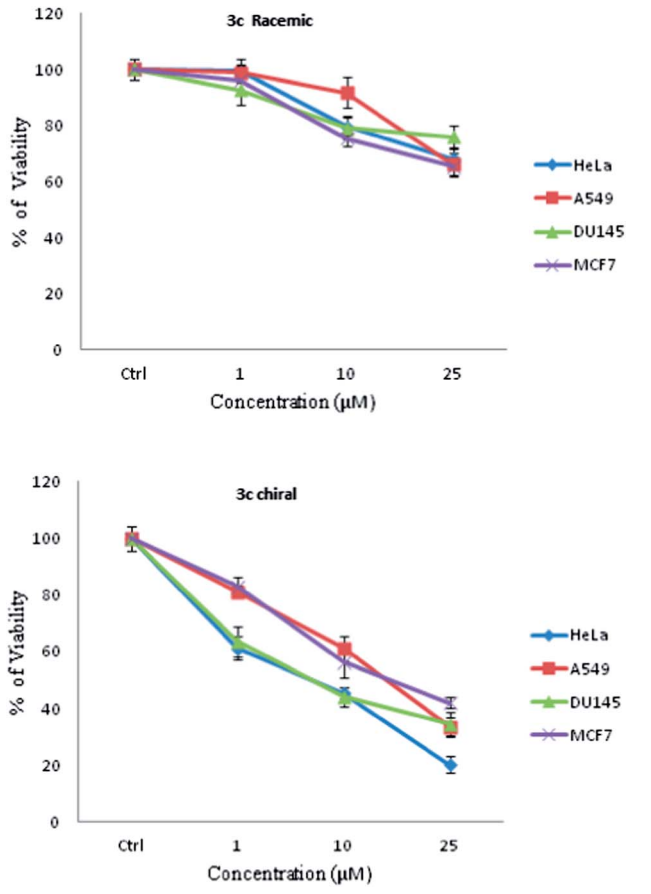


Fig. 3 Effect of chiral and racemic forms of **3c** on cell viability. Four different cancer cell lines were treated with compounds in concentration dependent manner (1 μM, 10 μM, 25 μM) for 48 h in 96 well plate followed by MTT assay.

Experimental

General. All reactions were carried out under nitrogen atmosphere. Commercial reagents were used as received, unless otherwise stated. ^{1}H NMR spectra were recorded on 300 MHz or 500 MHz spectrometer using $CDCl_3$ and DMSO-d_6 as a solvent. ^{13}C NMR were recorded on 75 MHz and 125 MHz spectrometer using $CDCl_3$ and DMSO-d_6. TMS was used as an internal reference for ^{1}H NMR analysis. All the compounds were purified by column chromatography on silica gel (60–120 mesh) using hexane–ethyl acetate mixture as eluent. Mass analysis was carried out using ESI mass spectrometer. Infrared (IR) spectra were recorded on FT-IR spectrometer. Optical rotations were measured using Rudolph (Digipol 781 M6U) polarimeter. The ee values were determined by chiral high-performance liquid chromatography (HPLC) using Daicel Chiracel OJ-H.

Materials and methods

Cell culture and maintenance

All cell lines used in this study were purchased from the American Type Culture Collection (ATCC). A549m (human lung carcinoma epithelial) and HeLa (human epithelial cervical cancer) were grown in Dulbecco's modified Eagle's medium (DMEM) containing non-essential amino acids and 10% FBS. MCF-7 (human breast adenocarcinoma) and DU145 (human prostate carcinoma epithelial) cells were cultured in Eagle's minimal essential medium (MEM) containing non-essential amino acids, 1 mM sodium pyruvate, and 10% FBS. All cell lines maintained in humidified atmosphere of 5% CO_2 at 37 °C. Cells were trypsinized when sub confluent from T75 flasks per 90 mm dishes and seeded in 96 well plate at a concentration of 1×10^4 cells mL^{-1} in complete medium, treated with compounds at desired concentrations and harvested as required.[17]

Cell proliferation assay using MTT

The assay is a quantitative colorimetric method for the determination of cell survival and proliferation. Metabolically active cells reduce pale yellow tetrazolium salt (MTT) to a dark blue water-insoluble formazan, which is quantified after solubilisation with DMSO. The absorbance of the solubilized formazan directly correlates with a number of viable cells. Cells were plated at a

density of 1×10^4 cells in 200 μL of medium per well of 96-well plate. The 96-well microtiter plate was incubated for 24 h prior to addition of the experimental compounds. Cells were treated at different concentrations (1, 10 and 25 μM) of the test compounds for 48 hours. The assay was terminated with the addition of MTT (5%, 10 μL) and incubated for 60 min at 37 °C. The supernatant was aspirated and plates were air dried. MTT-formazon crystals were dissolved in 100 μL DMSO. The optical density (O.D) was measured at 560 nm using TECAN multimode reader. The growth percentage of each treated well of 96 well plate was calculated based on test wells relative to control wells. The cell growth inhibition of compounds was analyzed by generating dose response curves as a plot of the percentage of surviving cells *versus* drug concentration. Anticancer activity of the cancer cells to the test compounds was articulated in terms of IC_{50} value, which defines as a concentration of compound resulting in the reduction of absorbance to 50% with respect to controls.[18]

Acknowledgements

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