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ARTICLE TYPE

Highly enantioselective Michael addition of diethyl malonate to chalcones catalyzed by *cinchona* alkaloids-derivatived bifunctional tertiary amine-thioureas bearing multiple hydrogen-bonding donors

Yu-Long Liu, Xie Wang, Xiao-Yun Wang and Wei He*

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Chalcones are still challenge substrates in the Michael reactions, and only limited success has been achieved. This work describe a highly enantioselective Michael addition of diethyl malonate with chalcones catalyzed by *cinchona* alkaloids-derivatived bifunctional tertiary amine-thioureas bearing multiple hydrogen-bonding donors.

The formation of carbon-carbon bonds by Michael addition of appropriate carboanionic reagents to α,β -unsaturated carbonyl compounds is one of the most useful methods of remote functionalization in organic synthesis.¹ Therefore, their catalytic asymmetric version have been studied extensively.² 2-(3-Oxo-1,3-arypropyl)malonic acids, prepared from the Michael adducts of malonates to chalcones, are allosteric modulators for the protein kinase C-related kinase 2 (PRK2)-interacting fragment (PIF) pocket of phosphoinositide-dependent kinase-1 (PDK1), and targeting the PIF pocket is possibly a novel approach for the treatment of diabetes type 2.³ Many kinds of catalysts, such as chiral phase transfer catalysts,⁴ chiral ionic liquids,⁵ chiral N,N'-dioxide-Sc complexes,⁶ chiral bis-sulfonamide-Sr complexes,⁷ chiral bisphosphazide-Li complexes,⁸ chiral SIPAD-Co complexes,⁹ DPEN/NAP-MgO,¹⁰ and organocatalysts,¹¹ have been developed for enantioselective Michael addition of malonates with chalcones. However, of them, some catalysts could not give satisfactory enantioselectivity; chalcones are still challenge substrates in the Michael reactions with malonates. Moreover, the scope of chalcones in the reported asymmetric Michael addition is very limited.

Asymmetric organocatalysis has emerged as one of the most rapidly growing and promising areas in synthetic organic chemistry.¹² Compared to traditional metal catalysis and biocatalysis, the advantages of organocatalysis include their operational simplicity and employment of readily available, low-cost, and low toxic organocatalysts. Previously, we developed a series of *cinchona* alkaloids-based bifunctional tertiary amine-thioureas bearing multiple hydrogen-bonding donors **1-4** (Figure 1) for highly enantioselective aza-Henry reaction, Michael additions of acetylactone and acetone to nitroolefins.¹³ The additional hydroxyl group in **1-4** might facilitate the formation of more hydrogen bonds and thereby significantly enhance the catalytic activity as well as the rigidity of the transition state, leading to high enantioselectivity and activity.¹⁴ Extending the

interest of these organocatalysts in asymmetric catalysis, herein, we describe a highly enantioselective Michael addition of diethyl malonate with chalcones catalyzed by *cinchona* alkaloids-derivatived bifunctional tertiary amine-thioureas bearing multiple hydrogen-bonding donors.

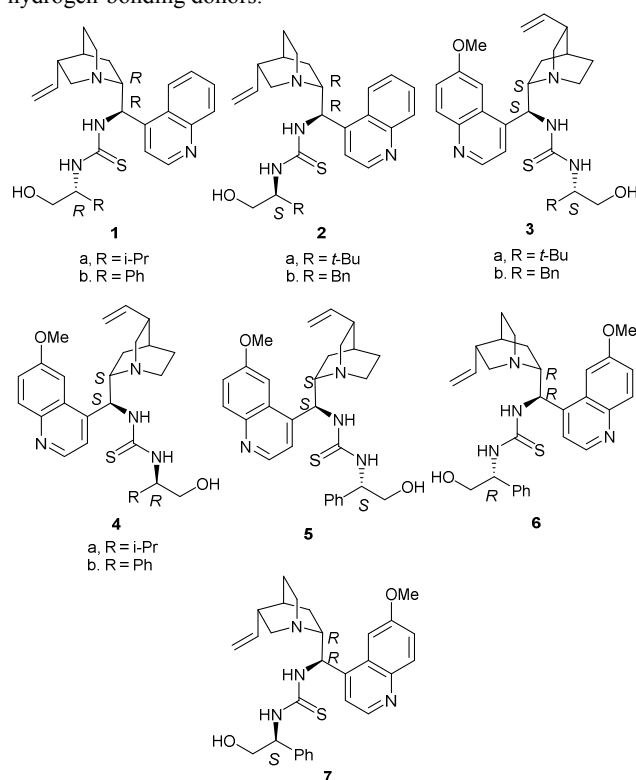
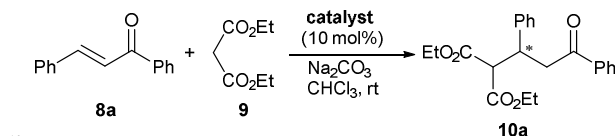


Figure 1. The *cinchona* alkaloids-based bifunctional tertiary amine-thioureas bearing multiple hydrogen-bonding donors.

Initially, the Michael addition of chalcone (**8a**) with diethyl malonate (**9**) was chose as model reaction for the screen of catalysts and reaction conditions. After extensive screening (see supporting information), to our delight, among the catalysts tested, **4b** showed a promising result. Thus, using 10 mol% of **4b** as catalyst, 1 equivalent of Na_2CO_3 as additive and CHCl_3 as solvent, chalcone (**8a**) reacted with diethyl malonate (**9**) at room temperature to give the adduct (*R*-**10a**) in 35% yield and 87% ee. Another three diastereoisomers **5**, **6** and **7** (Figure 2) were then

synthesized. The diastereomers **5** (from quinine and L-phenylglycine) and **6** (from quinidine and D-phenylglycine) are mismatched, giving almost racemate in the reaction. **7** (from quinidine and L-phenylglycine), a *pseudo*-enantiomer of **4b**, gave the product in similar enantioselectivity to **4b** but with opposite sense of asymmetric induction.

Table 1. Catalyst **4b** and its diastereoisomers in the asymmetric Michael reaction of chalcone with diethyl malonate^a



Entry	Catalyst	Yield (%) ^b	ee (%) ^{c,d}
1	4b	35	87 (<i>R</i>)
2	5	30	8 (<i>R</i>)
3	6	30	7 (<i>S</i>)
4	7	35	84 (<i>S</i>)

^aReaction conditions: 0.1 mmol of chalcone, 0.12 mmol of diethyl malonate, 10 mol% of catalyst and 100 mol % of Na₂CO₃ as base additive in 0.5 mL of CHCl₃ at room temperature for 48 h. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dAbsolute configuration was determined by comparison of the optical rotation with the value previously reported.⁷

Table 2. Effects of the base and temperature on the asymmetric Michael reaction catalyzed by catalyst **4b**^a

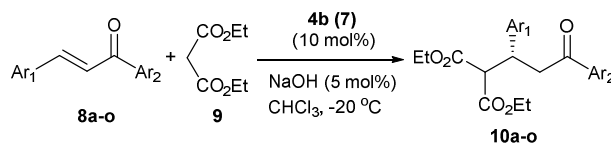
Entry	Base (mol%)	Temp. (°C)	Time (h)	Yield (%) ^b	ee (%) ^{c,d}
1	--	25	48	0	ND
2	K ₂ CO ₃ (100)	25	8	99	0
3	CS ₂ CO ₃ (100)	25	8	99	0
4	KOH (100)	25	8	99	0
5	Mg(OH) ₂ (50)	25	48	32	8
6	Ca(OH) ₂ (50)	25	48	20	13
7	Na ₂ CO ₃ (100)	25	48	35	87
8	NaOH (20)	25	8	99	10
9	NaOH (20)	0	8	99	44
10	NaOH (20)	-20	8	99	78
11	NaOH (10)	-20	8	99	85
12	NaOH (5)	-20	8	99	94

^{a,b,c,d}See the notes of Table 1.

Considering the significant effects of basic additives¹⁵ and reaction temperature on the enantioselectivity of Michael addition, the reaction conditions were optimized. As depicted in

Table 2, without a basic additive, the reaction cannot be promoted by a catalyst (entry 1). Then a variety of bases were tested as additives. When 1 equivalent K₂CO₃, CS₂CO₃ and KOH was added respectively, the reaction proceeded rapidly at room temperature and gave the adduct in almost quantitative yield but in racemate (entries 2-4). Low activity and low chiral induction were observed when 0.5 equivalent Mg(OH)₂ and Ca(OH)₂ were used (entries 5-6). High enantioselectivity but low yield were obtained with Na₂CO₃ as additive (entry 7). When NaOH was added, high activity was achieved, even in a lower loading (entry 8). Then, the effect of reaction temperature on the reaction was investigated. Lowering temperature significantly improved the enantioselectivity (entries 8-10). Finally, at -20°C, the amount of base were further optimized (entries 11-12). To our delight, high yield and excellent enantioselectivity were achieved when the reaction was performed in CHCl₃ at -20 °C using 10 mol% of **4b** as catalyst and 5 mol % of NaOH as additive (entry 12).

Table 3. The asymmetric Michael reaction of chalcones with diethyl malonate catalyzed by catalyst **4b** and 7^a



Entry	Ar ₁	Ar ₂	Yield (%) ^{b,d}	Ee (%) ^{c,d}
1	Ph	Ph (8a)	99 (97)	94 (-94)
2	3-CH ₃ C ₆ H ₄	Ph (8b)	95 (95)	92 (-92)
3	4-CH ₃ C ₆ H ₄	Ph (8c)	97 (98)	94 (-94)
4	2-CH ₃ OC ₆ H ₄	Ph (8d)	98 (99)	92 (-94)
5	4-CH ₃ OC ₆ H ₄	Ph (8e)	94 (93)	94 (-90)
6	2-CF ₃ C ₆ H ₄	Ph (8f)	95 (96)	93 (-96)
7	4-CF ₃ C ₆ H ₄	Ph (8g)	98 (98)	95 (-94)
8	2-ClC ₆ H ₄	Ph (8h)	96 (95)	96 (-96)
9	3-ClC ₆ H ₄	Ph (8i)	98 (99)	92 (-99)
10	4-ClC ₆ H ₄	Ph (8j)	99 (94)	94 (-90)
11	3-BrC ₆ H ₄	Ph (8k)	97 (99)	90 (-90)
12	4-BrC ₆ H ₄	Ph (8l)	89 (90)	93 (-90)
13	4-FC ₆ H ₄	Ph (8m)	99 (99)	92 (-90)
14	2-Furyl	Ph (8n)	87 (85)	91 (-91)
15	1-Naphthyl	Ph (8o)	80 (83)	94 (-95)
16	Ph	4-CH ₃ C ₆ H ₄ (8p)	96 (95)	94 (-94)
17	Ph	4-CH ₃ OC ₆ H ₄ (8q)	98 (96)	96 (-94)
18	Ph	4-CF ₃ C ₆ H ₄ (8r)	99 (98)	95 (-90)
19	Ph	4-ClC ₆ H ₄ (8s)	96 (97)	96 (-91)
20	Ph	4-FC ₆ H ₄ (8t)	99 (99)	95 (-90)
21 ^e	Ph	Ph (8a)	99 (97)	93 (-92)

^aUnless otherwise specified, the reactions were performed with 0.1 mmol of chalcone, 0.12 mmol of diethyl malonate, 10 mol% of **4b** and 5 mol % of NaOH in 0.5 mL of CHCl₃ at -20 °C for 8 h. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dThe data in parentheses were obtained by replacement of **4b** with **7** at -50 °C for 10 h. ^e5 mol% of catalyst was used.

Under the optimized reaction conditions, the substrate scope was subsequently investigated for this enantioselective Michael addition. A variety of substituted chalcones **8** reacted smoothly with diethyl malonate **9** to afford the corresponding products (*R*)-

10 in high yields (83–99%) and excellent enantioselectivities (90–97% ee) in the presence of 10 mol% of catalyst **4b** at -20 °C within 8 h (Table 3, entries 1–20). It appears that the position and the electronic property of the substituents on the aromatic rings have a very limited effect on the enantioselectivities. The heteroaryl and naphthyl derived α,β -unsaturated ketones also gave high yields and enantioselectivities (entries 14–15). Importantly, replacement of **4b** with its *pseudo*-enantiomer **7** gave the adduct (*S*)-**10** (with opposite configuration) in similar yields and enantioselectivities (entries 1–20, the data in parentheses). More importantly, the catalysts **4b** and **7** are highly active for the Michael addition as well. Almost identical results were obtained when the catalyst loading reduced from 10 mol% to 5 mol % (entry 1 vs. 21). It is worth noting that some adducts and their enantiomers are unknown compounds, such as **10b**, **10d**, **10f**, **10g**, **10i**, **10k**, **10l** and **10m**.

To explain the stereochemical outcome, plausible transition state (TS) models for the Michael reactions of chalcone **8a** and diethyl malonate **9** catalyzed by **4b** (TS **A**) and **7** (TS **B**) are proposed (Figure 2). In transition state **A**, the carbonyl group of chalcone is activated by the multiple hydrogen bonding interactions between the oxygen atom of the carbonyl with the thiourea moiety and the extra hydroxyl group of **4b**. Meanwhile diethyl malonate **9** is deprotonated by the basic nitrogen atom of the quinuclidine in *cinchona* alkaloid moiety. The excellent chiral environment of *cinchona* alkaloid backbone and the matched amino alcohol moiety enable diethyl malonate to attack the activated chalcone from *Si*-face, affording the *R*-configured product. While in transition state **B**, the Michael reactions of chalcone **8a** and diethyl malonate **9** was catalyzed by **7**, and a *Re*-face attack is favored, giving the *S*-configured product.

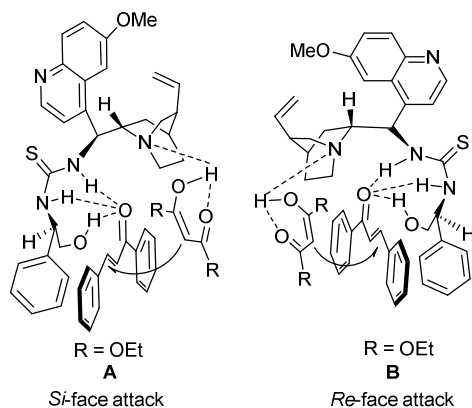


Figure 2. Plausible transition state for the enantioselective Michael reaction.

Conclusions

In summary, the bifunctional chiral tertiary amine-thioureas bearing multiple hydrogen-bonding donors **4b** and **7**, easily prepared from natural *cinchona* alkaloids and chiral amino alcohols, are highly effective in the asymmetric Michael additions of diethyl malonate to chalcones. Notably, catalyst **4b** and **7** showed similar catalytic activities and enantioselectivities, giving the *R* and *S* enantiomers of the adducts easily in up to 99%

yield and 99% ee. Further detailed catalytic mechanism and catalytic performance in other asymmetric reactions using this type of bifunctional tertiary amine-thioureas are currently underway in our laboratory.

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Notes and references

Department of Chemistry, School of Pharmacy, Fourth Military Medical University, Xi'an 710032, P. R. China. Fax: +86 29 84774470; Tel: +86 29 84774470; E-mail: weihechem@fmmu.edu.cn

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