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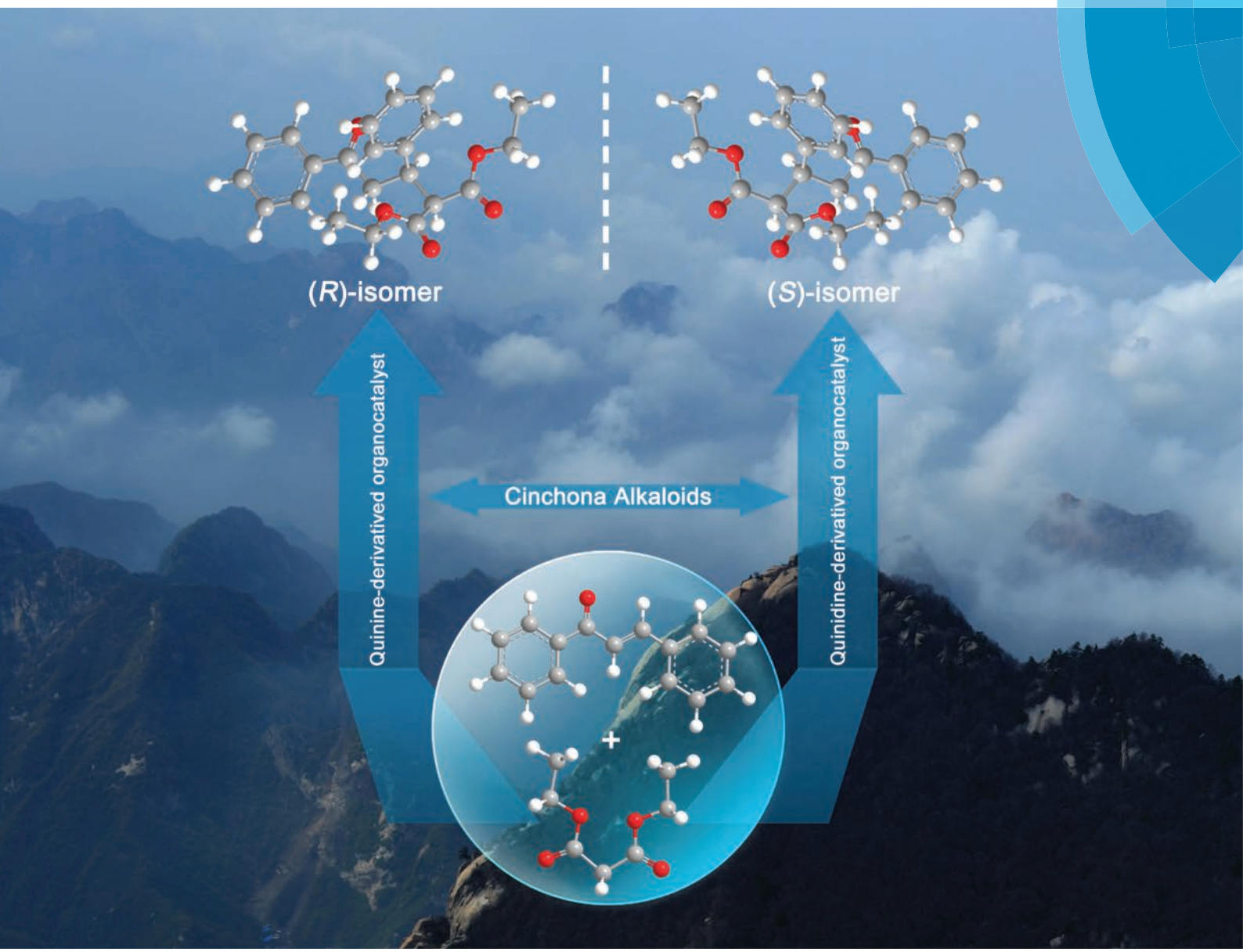

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Highly enantioselective Michael addition of diethyl malonate to chalcones catalyzed by *cinchona* alkaloids-derivatived bifunctional tertiary amine-thioureas bearing multiple hydrogen-bonding donors†

Yulong Liu, Xie Wang, Xiaoyun Wang and Wei He*

Chalcones are still challenge substrates in Michael reactions, and only limited success has been achieved. This work describes 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 the 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 has been studied extensively.[2] 2-(3-Oxo-1,3-arylpropyl)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 type 2 diabetes.[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, some of these catalysts could not give satisfactory enantioselectivity; chalcones are still challenging substrates in Michael reactions with malonates. Moreover, the scope of chalcones in reported asymmetric Michael additions 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 oganocatalysts. Previously, we developed a series of *cinchona* alkaloids-based bifunctional tertiary amine-thioureas bearing multiple hydrogen-bonding donors **1–4** (Fig. 1) for highly enantioselective aza-Henry reactions, Michael additions of acetylacetone and acetone to nitroolefins.[13] The additional hydroxyl group in **1–4** might facilitate the formation of more hydrogen bonds and thereby

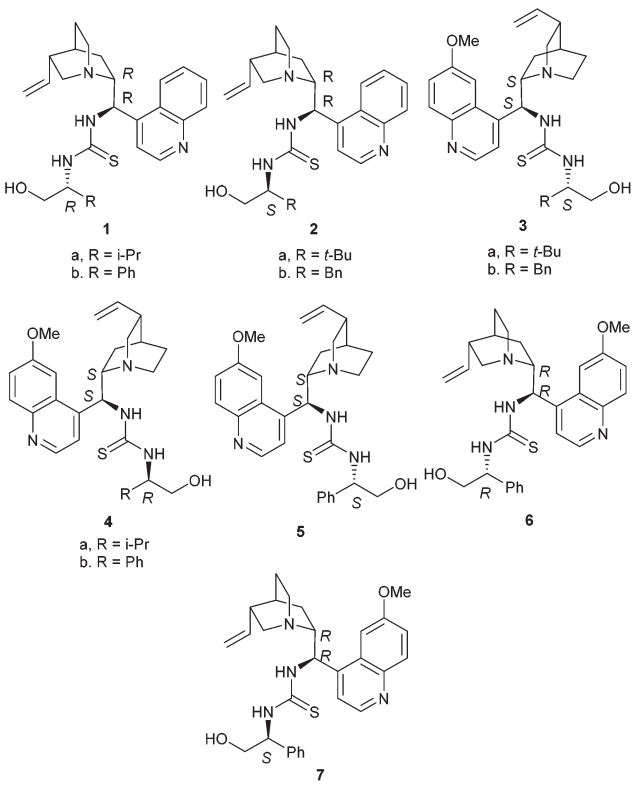

Fig. 1 The *cinchona* alkaloids-based bifunctional tertiary amine-thioureas bearing multiple hydrogen-bonding donors.

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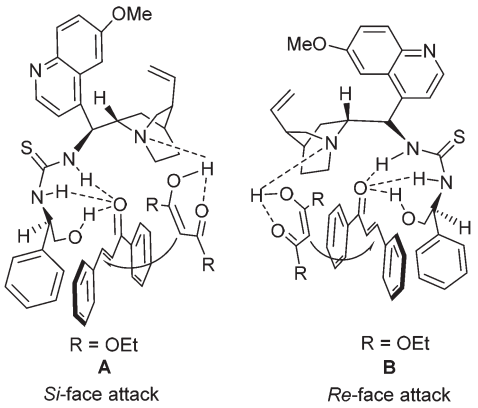


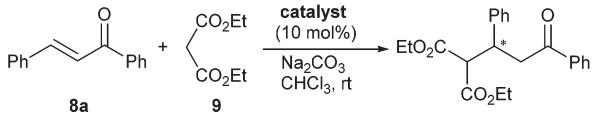
Fig. 2 Plausible transition state for the enantioselective Michael reaction.

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.

Initially, the Michael addition of chalcone (**8a**) with diethyl malonate (**9**) was chosen as model reaction for the screening of catalysts and reaction conditions. After extensive screening (see ESI†), 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** (Fig. 2) were then synthesized. Diastereomers **5** (from quinine and L-phenylglycine) and **6** (from quinidine and D-phenylglycine) are mismatched, giving almost a 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 asymmetric induction (Table 1).

Considering the significant effects of basic additives[15] 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 K_2CO_3, CS_2CO_3 and KOH was added respectively, the reaction proceeded rapidly at room temperature and gave the adduct in almost quantitative yield but as a 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 Na_2CO_3 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 the temperature significantly improved the enantioselectivity (entries 8–10). Finally, at −20 °C, the amount of base was further

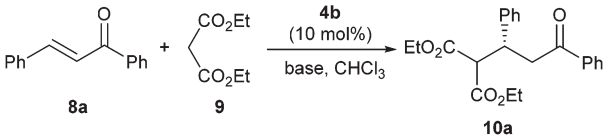
Table 1 Catalyst **4b** and its diastereoisomers in the asymmetric Michael reaction of chalcone with diethyl malonate[a]



Entry	Catalyst	Yield[b] (%)	ee[c,d] (%)
1	**4b**	35	87 (*R*)
2	**5**	30	8 (*R*)
3	**6**	30	7 (*S*)
4	**7**	35	84 (*S*)

[a] *Reaction conditions*: 0.1 mmol of chalcone, 0.12 mmol of diethyl malonate, 10 mol% of catalyst **4b** and 100 mol% of Na_2CO_3 as base additive in 0.5 mL of $CHCl_3$ at room temperature for 48 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Absolute 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]



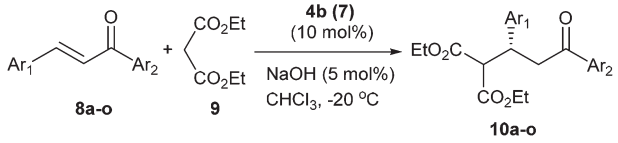
Entry	Base (mol%)	Temp. (°C)	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	—	25	48	0	ND
2	K_2CO_3 (100)	25	8	99	0
3	Cs_2CO_3 (100)	25	8	99	0
4	KOH (100)	25	8	99	0
5	$Mg(OH)_2$ (50)	25	48	32	8
6	$Ca(OH)_2$ (50)	25	48	20	13
7	Na_2CO_3 (100)	25	48	35	87
8	NaOH (20)	25	8	99	10
9	NaOH (20)	0	8	99	44
10	NaOH (20)	−20	8	99	78
11	NaOH (10)	−20	8	99	85
12	NaOH (5)	−20	8	99	94

[a] *Reaction conditions*: 0.1 mmol of chalcone, 0.12 mmol of diethyl malonate, 10 mol% of catalyst **4b** and 100 mol% of Na_2CO_3 as base additive in 0.5 mL of $CHCl_3$ at room temperature for 48 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Absolute configuration was determined by comparison of the optical rotation with the value previously reported.[7]

optimized (entries 11–12). To our delight, high yield and excellent enantioselectivity were achieved when the reaction was performed in $CHCl_3$ at −20 °C using 10 mol% of **4b** as catalyst and 5 mol% of NaOH as additive (entry 12).

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

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-$CH_3C_6H_4$	Ph (**8b**)	95 (95)	92 (−92)
3	4-$CH_3C_6H_4$	Ph (**8c**)	97 (98)	94 (−94)
4	2-$CH_3OC_6H_4$	Ph (**8d**)	98 (99)	92 (−94)
5	4-$CH_3OC_6H_4$	Ph (**8e**)	94 (93)	94 (−90)
6	2-$CF_3C_6H_4$	Ph (**8f**)	95 (96)	93 (−96)
7	4-$CF_3C_6H_4$	Ph (**8g**)	98 (98)	95 (−94)
8	2-ClC_6H_4	Ph (**8h**)	96 (95)	96 (−96)
9	3-ClC_6H_4	Ph (**8i**)	98 (99)	92 (−99)
10	4-ClC_6H_4	Ph (**8j**)	99 (94)	94 (−90)
11	3-BrC_6H_4	Ph (**8k**)	97 (99)	90 (−90)
12	4-BrC_6H_4	Ph (**8l**)	89 (90)	93 (−90)
13	4-FC_6H_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-$CH_3C_6H_4$ (**8p**)	96 (95)	94 (−94)
17	Ph	4-$CH_3OC_6H_4$ (**8q**)	98 (96)	96 (−94)
18	Ph	4-$CF_3C_6H_4$ (**8r**)	99 (98)	95 (−90)
19	Ph	4-ClC_6H_4 (**8s**)	96 (97)	96 (−92)
20	Ph	4-FC_6H_4 (**8t**)	99 (99)	95 (−90)
21[e]	Ph	Ph (**8a**)	99 (97)	93 (−92)

[a] Unless 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 $CHCl_3$ at −20 °C for 8 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The data in parentheses were obtained by replacement of **4b** with **7** at −50 °C for 10 h. [e] 5 mol % of catalyst was used.

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 was 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 (Fig. 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 the *cinchona* alkaloid backbone and the matched amino alcohol moiety enable diethyl malonate to attack the activated chalcone from the *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.

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 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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