Asymmetric Catalysis

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Direct Catalytic Asymmetric Mannich Reaction with Dithiomalonates as Excellent Mannich Donors: Organocatalytic Synthesis of (*R*)-Sitagliptin

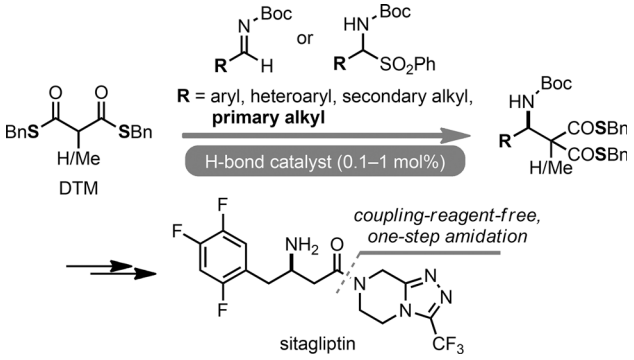
*Han Yong Bae, Mun Jong Kim, Jae Hun Sim, and Choong Eui Song**

Abstract: *In this study, dithiomalonates (DTMs) were demonstrated to be exceptionally efficient Mannich donors in terms of reactivity and stereoselectivity in cinchona-based-squaramide-catalyzed enantioselective Mannich reactions of diverse imines or α-amidosulfones as imine surrogates. Owing to the superior reactivity of DTMs as compared to conventional malonates, the catalyst loading could be reduced to 0.1 mol% without the erosion of enantioselectivity (up to 99% ee). Furthermore, by the use of a DTM, even some highly challenging primary alkyl α-amidosulfones were smoothly converted into the desired adducts with excellent enantioselectivity (up to 97% ee), whereas the use of a malonate or monothiomalonate resulted in no reaction under identical conditions. The synthetic utility of the chiral Mannich adducts obtained from primary alkyl substrates was highlighted by the organocatalytic, coupling-reagent-free synthesis of the antidiabetic drug (−)-(R)-sitagliptin.*

The asymmetric "direct" Mannich reaction[1] of commercially available malonates with N-protected imines or their precursor N-protected α-amidosulfones facilitates the synthesis of β-amino diesters,[2–4] which can be readily transformed into valuable optically active compounds, such as β-amino acids[2a] and β-lactams.[4a] Although a number of useful catalytic asymmetric variants are available, the limited utility of existing catalytic methods may be due to several factors, including the relatively high catalyst loading due to the low reactivity of malonates as Mannich donors. In particular, the instability of some primary aliphatic imines owing to rapid imine–enamine tautomerization hampers their use.[2b]

We presumed that the use of highly reactive Mannich donors, such as thiomalonates, would enable the above-mentioned issues to be addressed. Recently, Wennemers and co-workers employed monothiomalonates (MTMs) as reactivity-enhanced malonate surrogates for an asymmetric Mannich reaction with N-protected imines.[5] By the use of MTMs, the catalyst loading could be reduced to 1 mol%. As another class of reactivity-enhanced thioester enolates, dithiomalonates (DTMs) were successfully introduced by Tan and co-workers in 2007 for asymmetric catalysis.[6] More recently, Ishihara and co-workers applied DTMs in Mannich reactions with aryl imines in the presence of a dimeric chiral calcium phosphate Lewis acid catalyst.[7] Quite recently, Wang et al. also utilized MTMs and DTMs in chiral Brønsted base catalyzed Mannich reactions of alkynyl imine precursors.[8] However, to our knowledge, catalytic enantioselective Mannich reactions of dithiomalonates with N-protected primary alkyl imines or alkyl α-amidosulfones have not been attempted to date.

Herein, we report that the use of a DTM as a Mannich donor enabled a highly enantioselective organocatalytic asymmetric Mannich reaction with unprecedentedly low catalyst loadings (up to >99% *ee* with a 0.1 mol% catalyst loading). Furthermore, with DTMs, extremely challenging primary alkyl α-amidosulfone substrates were smoothly converted into the desired adducts with excellent enantioselectivity (up to 97% *ee*). The synthetic utility of the chiral Mannich adducts obtained from primary alkyl substrates was highlighted by the first organocatalytic, coupling-reagent-free synthesis of the antidiabetic drug (−)-(*R*)-sitagliptin (Scheme 1).



Scheme 1. Direct catalytic asymmetric Mannich reactions with DTM as the enolate precursor. Bn = benzyl.

Our initial investigation of the asymmetric Mannich reaction of DTM **2** with the *N*-(*tert*-butoxycarbonyl)imine **1a** is summarized in Table 1. The effect of the catalyst structure on the reaction outcome was first investigated at a catalyst loading of 1 mol% in CH_2Cl_2. The quinine-derived squaramide catalysts **QN-SQA** and **HQN-SQA**, and the quinidine-derived squaramide catalysts **QD-SQA** and **HQD-SQA**,[9] showed the best results in terms of catalytic activity (>99% conversion) and enantioselectivity (up to 99% *ee*; Table 1, entries 3–7). Surprisingly, the reaction proceeded

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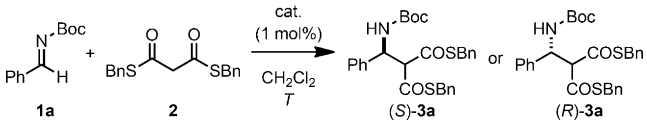
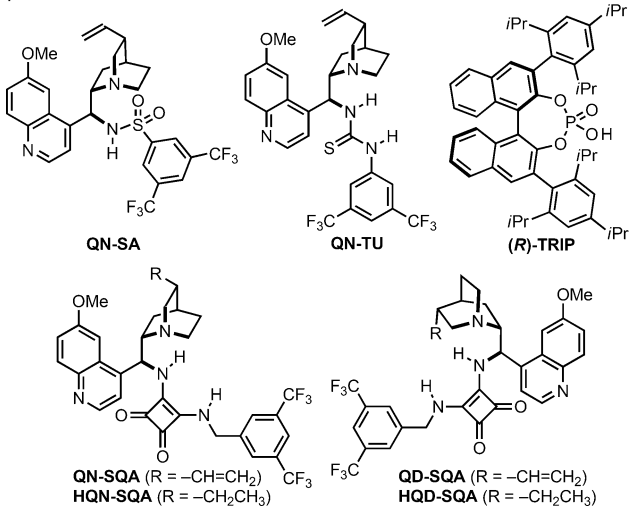
Table 1: Catalyst screening and solvent optimization.[a]



Entry	Catalyst	Solvent	*t* [min]	*T* [°C]	Conv. [%][b]	*ee* [%][c]
1	**QN-SA**	CH_2Cl_2	60	−50	69	0
2	**QN-TU**	CH_2Cl_2	60	−50	>99	74 (*R*)
3	**QN-SQA**	CH_2Cl_2	60	−50	>99	95 (*R*)
4	**HQN-SQA**	CH_2Cl_2	60	−50	>99	96 (*R*)
5	**QD-SQA**	CH_2Cl_2	60	−50	>99	99 (*S*)
6	**HQD-SQA**	CH_2Cl_2	60	−50	>99	99 (*S*)
7	**QD-SQA**	CH_2Cl_2	30	−15	>99	99 (*S*)
8	**QD-SQA**	CH_2Cl_2	10	0	>99	95 (*S*)
9	**QD-SQA**	CH_2Cl_2	<10	20	>99	75 (*S*)
10	**QD-SQA**	$CHCl_3$	60	−50	>99	99 (*S*)
11	**QD-SQA**	toluene	60	−50	>99	99 (*S*)
12	**QD-SQA**	THF	60	−50	>99	58 (*S*)
13	**QD-SQA**	acetone	60	−50	>99	41 (*S*)

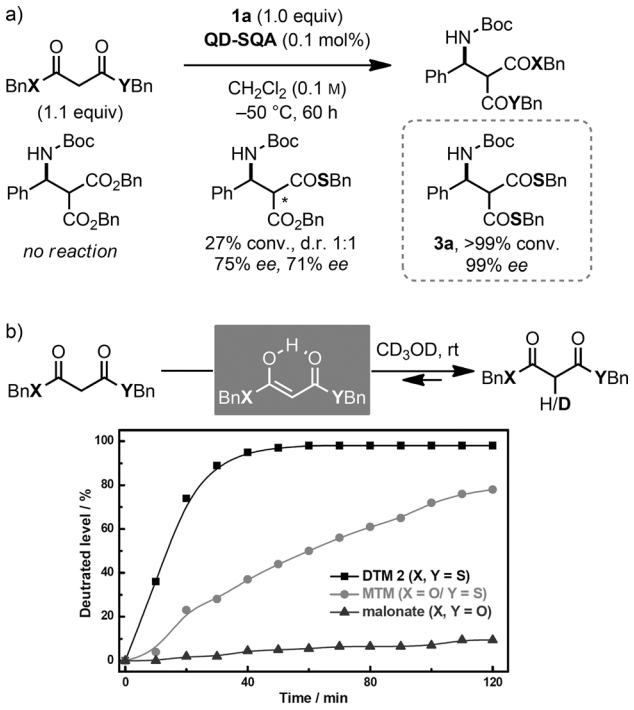
[a] Reactions were performed with **1a** (0.5 mmol), **2** (1.1 equiv), and a catalyst (1 mol%) in the solvent indicated (5.0 mL). [b] Conversion was determined by integration of the ^{1}H NMR spectrum of the crude product. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase.



extremely rapidly. At 0 °C, the reaction was completed within 10 min (entry 8), and even at a much lower temperature (−50 °C), full conversion was observed within 60 min into the desired Mannich product with excellent *ee* values (95% *ee* (*R*) and >99% *ee* (*S*)).[10] However, at room temperature, significantly lower enantioselectivity was observed owing to a rapid background reaction (entry 9).[11] The cinchona-based catalysts **QN-SA**[12] and **QN-TU**[13] showed inferior catalytic performance. With the quinine-based sulfonamide **QN-SA**, 69% conversion was observed with no enantioselectivity (Table 1, entry 1). The quinine-derived thiourea **QN-TU** demonstrated high catalytic activity but only moderate enantioselectivity (>99% conversion, 74% *ee*; Table 1, entry 2). Furthermore, in the presence of a Brønsted acid catalyst, the 1,1′-bi-2-naphthol-based phosphoric acid (*R*)-**TRIP**, which showed excellent performance in Mannich reactions of 1,3-diketones[14] and β-ketoesters,[7] showed no catalytic activity (for detailed experimental results on catalyst screening, see the Supporting Information).

Next, we examined the effect of the substrate structures on the reaction rate and enantioselectivity. Regardless of the type of protecting group (−CO_2tBu (−Boc), −CO_2Bn (−Cbz), or −CO_2Me), all imine substrates examined in this study were converted into the desired products smoothly with excellent enantioselectivity (97–99% yield, 95–99% *ee*; see the Supporting Information). The effect of the substituents (benzyl, ethyl, or phenyl) on the dithiomalonates in our reaction system was also investigated; among the substrates tested, the benzyl-substituted DTM **2** was the most suitable Mannich donor (up to 99% yield, up to 99% *ee*; see the Supporting Information). Other solvents were examined in further experiments. Chloroform and toluene were also suitable solvents (Table 1, entries 10 and 11). However, inferior asymmetric induction was observed in THF and acetone (entries 12 and 13).

To compare the relative reactivity of malonate derivatives, we carried out Mannich reactions of DTM **2**, dibenzyl monothiomalonate, and dibenzyl malonate with **1a** in the presence of 0.1 mol% of the **QD-SQA** catalyst. The comparative data in Scheme 2a indicate the superior reactivity of



Scheme 2. a) Relative reactivity of malonate derivatives. b) H/D exchange experiments.

the dithiomalonate relative to the monothiomalonate and the malonate. With DTM **2**, even a very low catalyst loading of 0.1 mol% resulted in full conversion and perfect enantioselectivity (99% *ee*). To our knowledge, this level of high reactivity with excellent enantioselectivity has not been reported previously in the field of the catalytic "direct introduction"[15] of ester and/or thioester enolates. In contrast,

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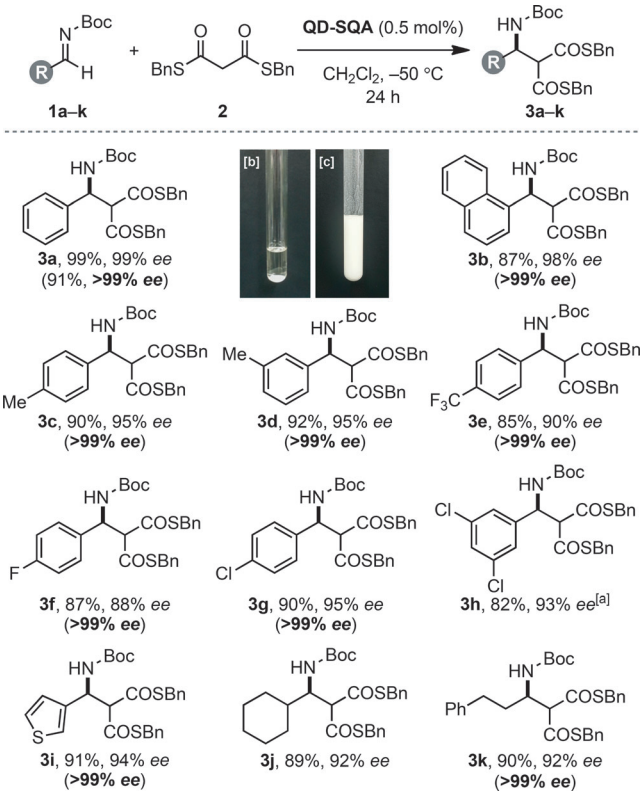
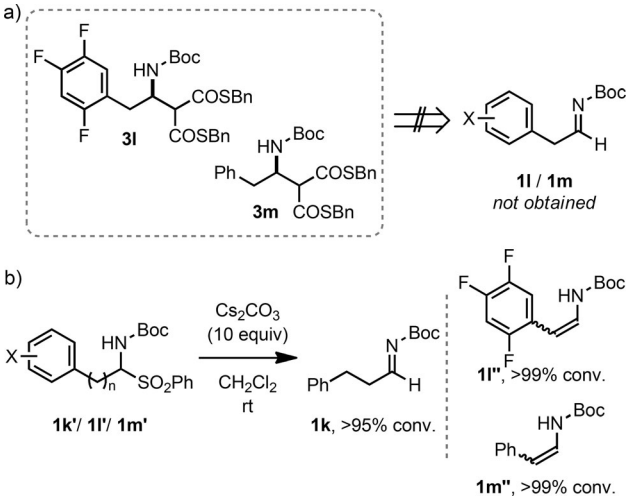
when the same reaction was performed with the monothiomalonate, 27% conversion and considerably lower stereoselectivity were observed (d.r. 1:1, 75 and 71% *ee*). Moreover, the dibenzyl malonate showed no reactivity under identical reaction conditions.[16] The superior reactivity of DTM **2** can be attributed to the significantly higher acidity of its α hydrogen atom than that of monothiomalonate and malonate. The relatively higher acidity of the α hydrogen atom in the dithiomalonate was determined by deuterium-exchange experiments of malonate derivatives (Scheme 2b).[17] DTM **2** dissolved in CD_3OD at room temperature showed 98% H/D exchange after 60 min, whereas the corresponding monothiomalonate and malonate displayed only 50 and 6% H/D exchange, respectively, at the same time point (for experimental details, see the Supporting Information).

A variety of aromatic, heteroaromatic, secondary alkyl, and primary alkyl aldimines were subjected to this protocol under the optimum reaction conditions, in the presence of 0.5 mol% of the catalyst **QD-SQA** (Scheme 3). Excellent enantioselectivity (88–99% *ee*) and chemical yields (85–99%) were observed. Enantiomerically pure products **3** could be readily obtained by direct recrystallization from the crude reaction mixture by adding hexane (see pictures in Scheme 3). However, this protocol is not applicable to the synthesis of some benzyl-substituted products, such as **3l** and **3m** (Scheme 4a), owing to the instability of the corresponding imines. For example, under the reported conditions[2b] for the preparation of N-protected imines, benzyl-substituted α-amidosulfones **1l′** and **1m′** were converted quantitatively into the unreactive enecarbamates (**1l″** and **1m″**) within 20 min (> 99%) as a result of rapid tautomerization, whereas the primary imine **1k** was successfully obtained from α-amidosulfone **1k′** (Scheme 4b; see the Supporting Information for the characterization of enecarbamates).



Scheme 3. Scope of the Mannich reaction of DTM **2** with *N*-Boc-protected imines **1**. Reactions were performed with **1** (0.5 mmol), **2** (1.1 equiv), and **QD-SQA** (0.5 mol%) in CH_2Cl_2 (5.0 mL) at −50 °C. The *ee* values in parentheses were observed after a single recrystallization from CH_2Cl_2/hexane at room temperature. [a] The reaction was carried out at −78 °C for 48 h. [b] Reaction mixture after completion of the Mannich reaction of **1a** with **2**. [c] Crude product mixture after the addition of hexane and stirring at room temperature. Enantiomerically pure (*S*)-**3a** was precipitated as a white solid: 91% yield, > 99% *ee*.



Scheme 4. a) Structures of desired primary-alkyl Mannich products **3l** and **3m**. b) Conversion of α-amidosulfones **1k′**,**1l′**, and **1m′** with a primary alkyl substituent under basic conditions.

To expand the reaction scope to challenging primary alkyl substrates, we implemented a one-pot Mannich reaction of bench-stable alkyl-substituted α-amidosulfones **1′** as imine surrogates with DTM **2** under aqueous biphasic conditions (Scheme 5; for experimental details of the optimization of conditions, see the Supporting Information). Owing to the superior reactivity of DTM **2**, enecarbamate formation was not observed, and thus α-amidosulfones **1l′** and **1m′** were successfully converted into the desired products **3l** and **3m** in high yields with high enantioselectivity (95 and 94% *ee*). Again, when dibenzyl monothiomalonate or dibenzyl malonate was employed as a Mannich donor, almost no conversion was observed. In particular, in the case of dibenzyl malonate, no product was observed even at a higher catalyst loading (10 mol%). Under the reaction conditions used, the amidosulfones **1l′** and **1m′** were converted into the unreactive enecarbamates **1l″** (88%) and **1m″** (91%), respectively (see the Supporting Information for details). Notably, other types of α-amido sulfones, **1n′**–**p′**, were also smoothly converted into the corresponding Mannich products, **3n**–**p**, in good to quantitative yield (80–95%) with excellent enantioselectivity (91–95% *ee*). In particular, the Mannich reaction of N-protected α-imino ethyl glyoxylate **1p**, generated in situ, highlights the remarkable synthetic utility of this method. Catalytic one-pot Mannich reactions of aldehydes or β-ketoesters as Mannich donors were reported by the research

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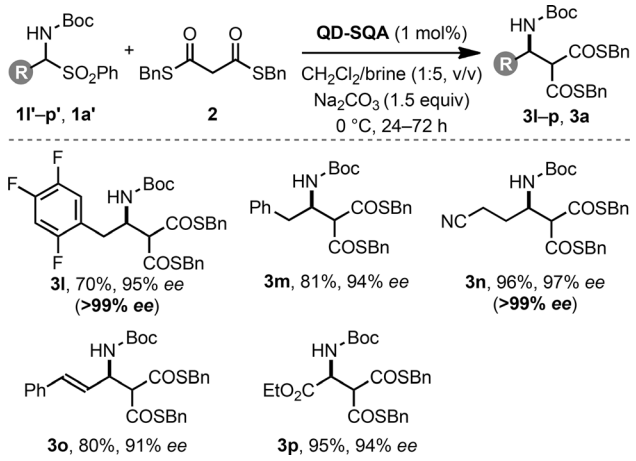
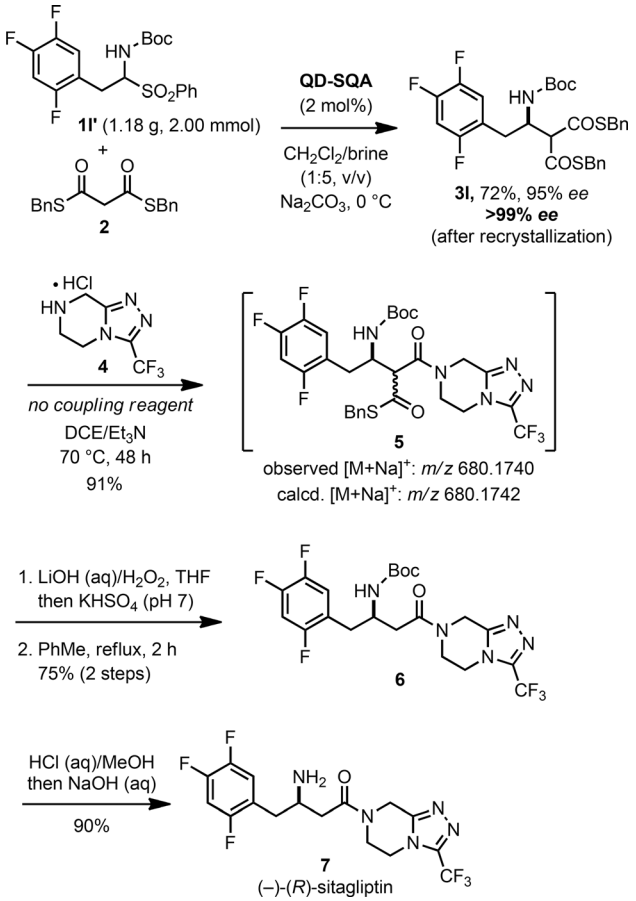


Scheme 5. Scope of the one-pot Mannich reaction of DTM **2** with *N*-Boc-protected α-amidosulfones **1′**. Reactions were performed with **1′** (0.5 mmol), **2** (1.1 equiv), Na_2CO_3 (1.5 equiv), and **QD-SQA** (1 mol%) in CH_2Cl_2 (1 mL)/brine (saturated NaCl solution, 5 mL) at 0°C. The *ee* values in parentheses were observed after a single recrystallization from CH_2Cl_2/hexane at room temperature.



Scheme 6. Organocatalytic synthesis of (*R*)-sitagliptin (**7**). DCE = 1,2-dichloroethane.

groups of Melchiorre[18a] and Jacobsen,[18b] respectively. However, a chiral thiomalonate-derived Mannich adduct, such as **3p**, which can be used as a building block for the synthesis of chiral α-amino acids and β-lactams, has not been reported previously.

The synthetic applicability of chiral Mannich adducts obtained from primary alkyl substrates was highlighted by the first organocatalytic, coupling-reagent-free synthesis of the antidiabetic drug (−)-(*R*)-sitagliptin. The phosphate salt of (−)-(*R*)-sitagliptin, which incorporates an aliphatic chiral β-amino amide backbone, is commercially available as a potent, orally active and selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus (T2DM).[19] This leading drug was approved by the US FDA in 2006, and is used as an active ingredient in monotherapy (Januvia) or in combination with metformin (Janumet). During the last decade, tremendous effort has focused on the development of diverse synthetic protocols for sitagliptin, by the asymmetric hydrogenation of β-ketoesters or β-enamines with transition-metal catalysts (e.g. PtO_2, Rh, and Ru).[19,20] Although the reported methods were efficient and scalable, high-pressure (250 psi) hydrogen gas and the removal of precious and toxic transition metals are essential. Later, a biocatalytic route through the direct reductive amination of a β-ketoester with a transaminase enzyme was reported.[21] This biocatalytic process was environmentally friendly and concise, and replaced the previous transition-metal-catalyzed process. However, as a "third pillar" of asymmetric catalysis, an organocatalytic route to sitagliptin is unprecedented. To demonstrate the synthetic utility of the newly established Mannich reaction, we performed a gram-scale synthesis of sitagliptin (Scheme 6). The one-pot Mannich reaction of **1l′** (1.18 g) with DTM **2** in the presence of **QD-SQA** (2 mol%) afforded the desired product (*R*)-**3l** (72%, 95% *ee*). The obtained product was recrystallized from CH_2Cl_2/hexane to afford enantiomerically pure (*R*)-**3l** (>99% *ee*). Next, **3l** was coupled with the commercially available triazole salt **4** without the use of any coupling reagent[5,22] to give amide **5** (91%), which was detected by ESI-HRMS analysis (observed: *m*/*z* 680.1740 $[M+Na]^+$; calcd: *m*/*z* 680.1742). The diastereomeric mixture of amide **5** was then transformed into *N*-Boc-protected sitagliptin, **6**, through hydrolysis and subsequent decarboxylation (75%). Finally, Boc deprotection under acidic conditions gave the target compound (−)-(*R*)-sitagliptin (**7**; 90%, $[\alpha]_D^{20} = -22.9$ ($c = 1.0$, $CHCl_3$); Lit.:[23] $[\alpha]_D^{25} = -23.3$ ($c = 1.0$, $CHCl_3$)).

In summary, we have developed highly enantioselective Mannich reactions with cinchona-based-squaramide organocatalysts, which afforded diverse chiral Mannich products in high yield with excellent enantioselectivity (up to 99% *ee*). Dibenzyl dithiomalonate (**2**) was a remarkably effective Mannich donor in terms of reactivity and stereoselectivity. Owing to the superior reactivity of dithiomalonate as compared to conventional malonate derivatives, the catalyst loading could be reduced to 0.1 mol% without erosion of enantioselectivity (99% *ee*). More importantly, the superior reactivity of dithiomalonates facilitated the reaction of several highly challenging substrates with primary alkyl substituents, which could not be used with less-reactive malonates and monothiomalonates. The synthetic utility of

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the chiral Mannich adducts obtained from primary alkyl substrates was highlighted by the first organocatalytic, coupling-reagent-free synthesis of the antidiabetic drug (−)-(*R*)-Sitagliptin.

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Keywords: β-amino thioesters · asymmetric catalysis · dithiomalonates · Mannich reaction · organocatalysis

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[10] The absolute configurations of products **3a** and **3k** obtained with the catalyst **QD-SQA** were determined to be *S* and *R*, respectively, by conversion into the corresponding *N*-Boc amino diesters (see Ref. [3b]). For analytical data and spectra, see the Supporting Information.

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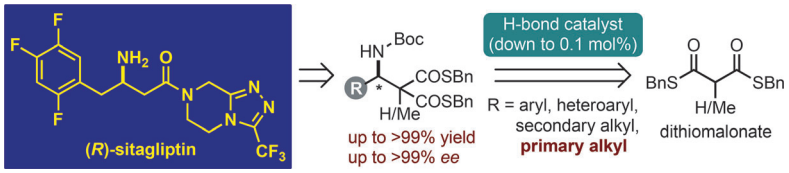
Communications

Asymmetric Catalysis

H. Y. Bae, M. J. Kim, J. H. Sim, C. E. Song* ——— ■■■■–■■■■

Direct Catalytic Asymmetric Mannich Reaction with Dithiomalonates as Excellent Mannich Donors: Organocatalytic Synthesis of (*R*)-Sitagliptin



The third pillar: The intrinsic limitation of asymmetric Mannich reactions—their failure with imine substrates containing a primary alkyl substituent—was solved by employing dithiomalonates as Mannich donors and a chiral squaramide organocatalyst. This protocol was used to develop a concise organocatalytic, coupling-reagent-free synthesis of the antidiabetic drug (−)-(*R*)-sitagliptin (see scheme).

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