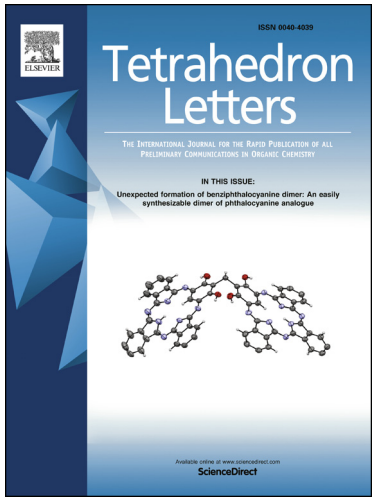

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Highly enantioselective Michael addition of α,α-disubstituted aldehydes to maleimides catalyzed by new primary amine-squaramide bifunctional organocatalysts

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ABSTRACT

New bifunctional primary amine-squaramides catalyzed asymmetric Michael addition reaction of α,α-disubstituted aldehydes to maleimides has been developed. This organocatalytic asymmetric reaction provides easy access to functionalized succinimides with a broad substrate scope. Both enantiomers of desired succinimide derivatives were obtained in good to excellent yields (up to 98%) with excellent enantioselectivities (up to >99% ee).

Introduction

The Michael reaction promoted by organocatalysts has been widely utilized for the efficient formation of C-C bond due to the value of the Michael adducts as synthetic building blocks [1]. Among the various unsaturated Michael acceptors, maleimides are an important class of substrates. The asymmetric organocatalytic functionalization of maleimides could produce chiral substituted succinimide derivatives which are widely distributed in natural products and pharmaceuticals [2]. As a result, much attention has been paid to the development of catalytic asymmetric Michael addition using maleimides as the substrates and impressive progress have been achieved [3].

In 2007, Córdova first described the asymmetric Michael reaction of aldehydes to maleimides catalyzed by diphenylprolinolsilyl ether with moderate yields and enantioselectivities obtained when sterically hindered α,α-disubstituted aldehydes were employed as the nucleophiles [4]. Since then, many types of chiral organocatalysts such as primary amine thioureas [5], 1,2-diamines [6], monoprotected 1,2-diamines [7], primary amine guanidines [8], primary amine 2-amino benzimidazole [9], and primary amine 2-amino pyrimidine [10] have been developed for this important carbon–carbon bond forming reaction. However, no report was described on this asymmetric reaction using chiral squaramide as catalyst to date.

Chiral squaramide is a novel type of H-bonding promoted asymmetric organocatalyst [11]. Since the pioneering work by Rawal in 2008 [12], who reported a chiral squaramide in the conjugated addition reactions of 1,3-dicarbonyl compounds to β-nitrostyrenes, squaramide-based organocatalysts have been widely utilized in various asymmetric reactions [13].

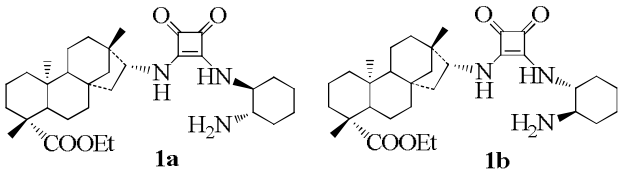

Figure 1. Chiral primary amine–squaramide

As part of our ongoing interest in the asymmetric organocatalysis [5h,14], we have demonstrated for the first time that the novel chiral primary amine–squaramide organocatalysts derived from commercially available natural product stevioside could promote the asymmetric conjugated addition of isobutyraldehyde to various nitroolefins at room temperature in high yields (up to 98%) with high to excellent enantioselectivities (up to 99% ee). This catalytic protocol provided both enantiomers of the corresponding products with almost the same ee value. Based on our previous work, and in order to broaden the application scope of the novel organocatalysts, we herein

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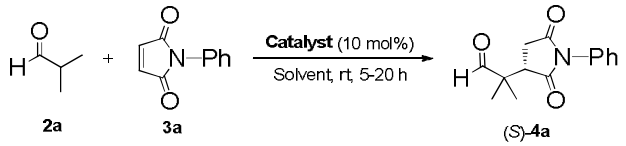
report the asymmetric Michael addition of α,α-disubstituted aldehydes to maleimides catalyzed by chiral primary amine-squaramide catalysts.

Results and Discussion

Table 1. Solvent screening [a]



Entry	Catalyst	Solvent	Yield (%)[b]	*ee* (%)[c]
1	**1a**	$CHCl_3$	87	98 (*S*)
2	**1b**	$CHCl_3$	71	97 (*R*)
3	**1a**	Ether	10	87 (*S*)
4	**1a**	THF	27	97 (*S*)
5	**1a**	Toluene	94	99 (*S*)
6	**1a**	CH_2Cl_2	86	98 (*S*)
7	**1a**	CH_3OH	22	11 (*S*)
8	**1a**	H_2O	24	28 (*S*)
9[d]	**1a**	Neat	86	82 (*S*)

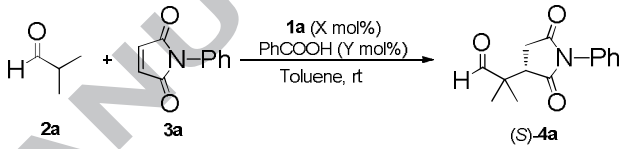
[a] Unless otherwise specified, all reactions were carried out using isobutyraldehyde (**2a**, 0.40 mmol), N-phenylmaleimide (**3a**, 0.20 mmol) and 10 mol% **1a** or **1b** in 1.0 mL solvent at room temperature for 5-20 h.
[b]Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 0.80 mmol isobutyraldehyde was used.

The efficacy of bifunctional amine-squaramides **1a** and **1b** as chiral organocatalysts was initially evaluated using the reaction of isobutylaldehyde and *N*-phenylmaleimide in $CHCl_3$ at room temperature (Table 1, entries 1-2). Under the same conditions, both the catalyst **1a** and **1b** gave the desired product **4a** in good yields with high enantioselectivities, as well as a reversal of the absolute configuration of product **4a**. These results indicate that both the (*S,S*) and the (*R,R*) configuration of 1,2-diaminocyclohexane moiety can well match the isosteviol scaffold of **1a** and **1b**. Furthermore, the configuration of 1,2-diaminocyclohexane moiety predominates the absolute configuration of product **4a**.

Next, various solvents were examined at room temperature using **1a** as the catalyst. When the reaction was carried out in ether and THF, poor yields were observed (Table 1, entries 3-4). In the case of toluene, the Michael adduct could be obtained in higher yield and excellent enantioselectivity (Table 1, entry 5). In dichloromethane, catalyst **1a** also efficiently promoted the reaction but the yield and ee value were almost the same as those in chloroform (Table 1, entry 6). Solvents such as MeOH and H_2O, which could disturb the H-bonding of **1a** with **3a**, reduced the yield and enantioselectivity dramatically (Table 1, entries 7-8). With respect to the neat condition, the reaction carried out smoothly to furnish the product in high yield with good enantioselectivity (Table 1, entry 9). A screen of solvents revealed that toluene was the most suitable solvent.

Subsequently, the effects of the catalyst loadings, additives, and reaction time were investigated. Surprisingly, lowing the catalyst loading from 10 mol% to 5 mol% did not affect the yield and enantioselectivity (Table 2, entries 1-2). Further decrease of the catalyst loading to 2 mol% did not affect the enantioselectivity, but the yield was diminished significantly (Table 2, entry 3). When the 1 mol% catalyst loading was employed, the reaction was very sluggish and only trace amount of the product was obtained (Table 2, entry 4). To make the organocatalyst more effective, the role of suitable additive, or co-catalyst, could be crucial in enhancing the reactivity and stereoselectivity of the catalytic system. For example, it has been shown that PhCOOH was often applied as an efficient promoter for the chiral thiourea catalyzed asymmetric Michael reaction.[6a,6b,8g-i,8k] To our delight, when PhCOOH was utilized as an additive, not only the reaction rate was dramatically accelerated, but the yield and enantioselectivity were promoted significantly(Table 2, entry 5). Encouraged by this result, we attempted to further decrease the catalyst loading to 0.5 mol%, the product was still obtained in high yield with excellent enantioselectivity (Table 2, entry 6). However, when the amount of catalyst was reduced to 0.2 mol%, the reaction was rather sluggish so that the yield was only 56% after 36 hours. (Table 2, entry 7). Taking into account the beneficial effects of benzoic acid on accelerating the reaction, 1.0 mol% PCOOH with 0.2 mol% **1a** were introduced as catalysts. The reaction was still proceeding slowly (Table 2, entry 8). 0.2 mol% catalyst was not applicable. Based on the above results, the optimal reaction conditions employed 0.40 mmol **2a** (2.0 equiv.) and 0.20 mmol **3a**(1.0 equiv.) as the substrates, 0.5 mol% PhCOOH as the additive, and 0.5 mol% **1a** or 1b as the catalyst in 1.0 mL toluene at ambient temperature for 12 h (Table 2, entry 9).

Table 2. Optimization of conditions [a]



Entry	X	Y	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	10	-	5	94	99 (*S*)
2	5	-	12	93	99 (*S*)
3	2	-	48	51	99 (*S*)
4	1	-	48	trace	nd[d]
5	1	1	5	95	99 (*S*)
6	0.5	0.5	12	95	>99 (*S*)
7	0.2	0.2	48	56	98 (*S*)
8	0.2	1.0	36	92	99 (S)
9[e]	0.5	0.5	12	98	>99 (*R*)

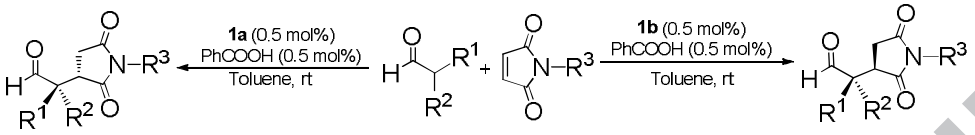
[a] Unless otherwise specified, all reactions were carried out using isobutyraldehyde (**2a**, 0.40 mmol) and *N*-phenylmaleimide (**3a**, 0.20 mmol) in 1.0 mL toluene at room temperature.
[b]Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Not determined.
[e] Catalyst **1b** was used.

With the optimized conditions in hand, the reaction of various isobutylaldehydes and *N*-phenylmaleimides were examined to explore the generality of this novel catalytic system, which are summarized in Tables 3. A broad range of *N*-aryl maleimide derivatives reacted smoothly with isobutylaldehyde in high yields with excellent enantioselectivities (Table 3, entries 1-22). Generally, substituents on the aromatic rings slightly influenced the yields and enantioselectivities. Electron-neutral (Table 3, entries 1-2), -withdrawing (Table 3, entries 3-16), and-donating (Table 3, entries 17-22) substituted *N*-phenylmaleimides were all well tolerated to provide highly enantioselective adducts. In the change to alkyl-substituted maleimides, benzyl maleimide **3l** and cyclohexyl maleimide **3m** were observed to perform similarly to aryl maleimides (Table 3, entries 23-26). We found that maleimide **3n** bearing no substituent group on the nitrogen atom was also effective reaction partner in the Michael reaction with isobutylaldehyde (Table 3, entries 27-28). It is clear that the product's enantioselectivity actually decreased more than a little compared to other substrates. The hydrogen of maleimide may

affect the H-bonding interaction between the catalyst and the substrate.

We next investigated the Michael reaction of other aldehydes to maleimide. For symmetrical α,α-disubstituted aldehyde, cyclohexyl formaldehyde **2b** reacted with maleimides smoothly, and the corresponding Michael adducts were obtained in good yields with excellent enantioselectivities (Table 2, Entries 29-38). Next, two nonsymmetrical aldehydes were utilized, since in this manner the formation of two contiguous (quaternary-tertiary) stereogenic centers will be possible (Table 2, Entries 39-42). In all cases, high yields and excellent enantioselectivities were obtained. Unfortunately, the dr was not very good, from 58/42 to 66/34.

Table 3. Substrate Scope of the Michael Addition [a]



4a-u **2a-d** **3a-p** **4a-u**

Entry	R^1,R^2	R^3	Cat.	Adduct	Yield (%)[b]	dr[c]	*ee* (%)[c]
1	Me, Me (**2a**)	C_6H_5 (**3a**)	**1a**	(*S*)-**4a**	97	-	99
2			**1b**	(*R*)-**4a**	98	-	>99
3	Me, Me (**2a**)	4-FC_6H_4 (**3b**)	**1a**	(*S*)-**4b**	91	-	99
4			**1b**	(*R*)-**4b**	95	-	>99
5	Me, Me (**2a**)	3-ClC_6H_4 (**3c**)	**1a**	(*S*)-**4c**	91	-	98
6			**1b**	(*R*)-**4c**	90	-	>99
7	Me, Me (**2a**)	4-ClC_6H_4 (**3d**)	**1a**	(*S*)-**4d**	92	-	98
8			**1b**	(*R*)-**4d**	95	-	>99
9	Me, Me (**2a**)	3-BrC_6H_4 (**3e**)	**1a**	(*S*)-**4e**	96	-	98
10			**1b**	(*R*)-**4e**	92	-	99
11	Me, Me (**2a**)	4-BrC_6H_4 (**3f**)	**1a**	(*S*)-**4f**	90	-	99
12			**1b**	(*R*)-**4f**	87	-	>99
13	Me, Me (**2a**)	3-$NO_2C_6H_4$ (**3g**)	**1a**	(*S*)-**4g**	89	-	98
14			**1b**	(*R*)-**4g**	92	-	>99
15	Me, Me (**2a**)	4-$NO_2C_6H_4$ (**3h**)	**1a**	(*S*)-**4h**	93	-	98
16			**1b**	(*R*)-**4h**	91	-	>99
17	Me, Me (**2a**)	4-$OCH_3C_6H_4$ (**3i**)	**1a**	(*S*)-**4i**	97	-	>99
18			**1b**	(*R*)-**4i**	97	-	>99
19	Me, Me (**2a**)	4-$CH_3C_6H_4$ (**3j**)	**1a**	(*S*)-**4j**	98	-	99
20			**1b**	(*R*)-**4j**	95	-	>99
21	Me, Me (**2a**)	2,6-$(CH_3)_2C_6H_3$ (**3k**)	**1a**	(*S*)-**4k**	90	-	>99
22			**1b**	(*R*)-**4k**	93	-	>99
23	Me, Me (**2a**)	$C_6H_5CH_2$ (**3l**)	**1a**	(*S*)-**4l**	95	-	>99
24			**1b**	(*R*)-**4l**	97	-	>99
25	Me, Me (**2a**)	*c*-hexyl (**3m**)	**1a**	(*S*)-**4m**	99	-	>99
26			**1b**	(*R*)-**4m**	99	-	>99
27	Me, Me (**2a**)	H (**3n**)	**1a**	(*S*)-**4n**	96	-	86
28			**1b**	(*R*)-**4n**	98	-	86
29	-$(CH_2)_5$- (**2b**)	C_6H_5 (**3a**)	**1a**	(*S*)-**4o**	97	-	98
30			**1b**	(*R*)-**4o**	98	-	>99
31	-$(CH_2)_5$- (**2b**)	4-FC_6H_4 (**3b**)	**1a**	(*S*)-**4p**	91	-	99
32			**1b**	(*R*)-**4p**	88	-	>99
33	-$(CH_2)_5$- (**2b**)	4-$CH_3C_6H_4$ (**3i**)	**1a**	(*S*)-**4q**	88	-	98
34			**1b**	(*R*)-**4q**	85	-	99
35	-$(CH_2)_5$- (**2b**)	2,6-$(CH_3)_2C_6H_3$ (**3j**)	**1a**	(*S*)-**4r**	90	-	97
36			**1b**	(*R*)-**4r**	86	-	97
37	-$(CH_2)_5$- (**2b**)	$C_6H_5CH_2$ (**3l**)	**1a**	(*S*)-**4s**	92	-	97
38			**1b**	(*R*)-**4s**	90	-	97
39	Me, Et (**2c**)	C_6H_5 (**3a**)	**1a**	(*S,S*)-**4t**	95	58/42	>99(>99)[d]
40			**1b**	(*R,R*)-**4t**	93	59/41	>99(>99)
41	Me, *n*-Pr (**2d**)	C_6H_5 (**3a**)	**1a**	(*S,S*)-**4u**	92	66/34	>99(>99)
42			**1b**	(*R,R*)-**4u**	98	65/35	>99(>99)

[a] Unless otherwise specified, all reactions were carried out using aldehyde (**2**, 0.40 mmol), maleimide (**3**, 0.20 mmol), 0.5 mol% **1a** or **1b** and 0.5 mol% PhCOOH in 1.0 mL toluene at room temperature.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis.

[d] Ee of the minor diastereomer in parentheses.

On the basis of the experimental results described above, a plausible transition-state model was proposed. As shown in Figure 2, the amino of bifunctional squaramide catalyst **1a** reacted with aldehyde to form an enamine and the squaramide activated maleimide via H-bonding interaction. The enamine attacked the maleimide from the *Re*-face to afford the product, which was consistent with the experimental results.

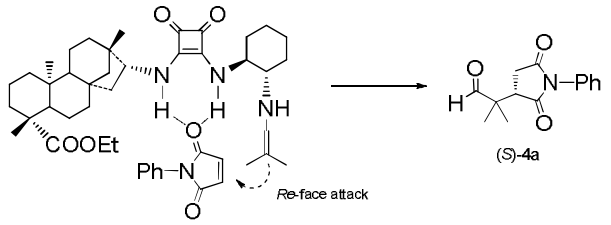


Figure 2. Proposed catalytic reaction mode.

Conclusion

In conclusion, we have shown that the novel isoteviol-based chiral primary amine squaramide catalysts are highly effective in the addition of α,α-disubstituted aldehydes with maleimides to generate versatile chiral substituted succinimide derivatives. Both enantiomers of the adducts were obtained in high yields and excellent enantioselectivities, which makes the current strategy potentially useful. Compared with isoteviol-derived thiourea catalyst[5h], squaramide catalyst **1a** and **1b** exhibited a higher catalytic reactivity; both the yields and enentioselectivities were improved. Further investigations on the application of these catalysts in asymmetric catalysis are in progress.

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Michael addition of α,α-disubstituted aldehydes to maleimides.

Bifunctional primary amine-squaramides were used as catalyst for this transformation.

Enantioselective synthesis of succinimide derivatives.

Graphical Abstract

Highly enantioselective Michael addition of α,α-disubstituted aldehydes to maleimides catalyzed by new primary amine-squaramide bifunctional organocatalysts

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