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Organocatalytic Enantioselective Cascade Aza-Michael/Michael Addition for the Synthesis of Highly Functionalized Tetrahydroquinolines and Tetrahydrochromanoquinolines

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Abstract: An efficient organocatalytic highly asymmetric cascade aza-Michael/Michael addition reaction for the synthesis of tetrahydroquinolines and tetrahydrochromanoquinolines has been developed. This cascade reaction proceeds well at low catalyst loading with a broad substrate scope, furnishing the desired products in excellent yields with excellent diastereoselectivities and enantioselectivities (up to >99:1 *dr*, 99% *ee*) under mild conditions. Importantly, it is the first catalytic asymmetric method for tetrahydrochromanoquinolines. This protocol provides a straightforward entry to highly functionalized chiral tetrahydroquinoline and tetrahydrochromanoquinoline derivatives from simple starting materials.

Keywords: cascade aza-Michael/Michael addition; organocatalysis; squaramide; tetrahydrochromanoquinolines; tetrahydroquinolines

Introduction

Tetrahydroquinoline and tetrahydrochromanoquinoline motifs are present in a number of natural and pharmaceutical products, possessing diverse biological activities.[1] Some typical examples are shown in Figure 1. For example, the simple tetrahydroquinoline angustureine, isolated from the bark of South American tree *Galipea officinalis*,[1c] shows anti-mycobacterial and anti-malarial activities.[1d] Martinellic acid and martinelline, extracted from the tropical plant *Martinella iquitosensis*, exhibit modest antibiotic activity as an eye medicine for conjunctivitis in South America and possess potent antagonist activity toward bradykinin (BK) receptors.[1e] L-689,560 is one of the most potent antagonists for the NMDA receptor glycine site.[1f] The tetrahydrochromanoquinoline derivative figured displays anti-proliferative activity comparable to that of tamoxifen on both MDA-MB-231 and MCF-7 breast cancer cells.[1g] Additionally, some tetrahydroquinoline derivatives have been employed as chiral ligands in asymmetric catalysis.[2]

In view of their great significance, tetrahydroquinolines[1a,b] and tetrahydrochromanoquinolines[3] have become attractive synthetic targets, and many efficient approaches have been established. However, there are only a few catalytic enantioselective methods for tetrahydroquinolines,[4,5] and none for tetrahydrochromanoquinolines. Among them, two reports on

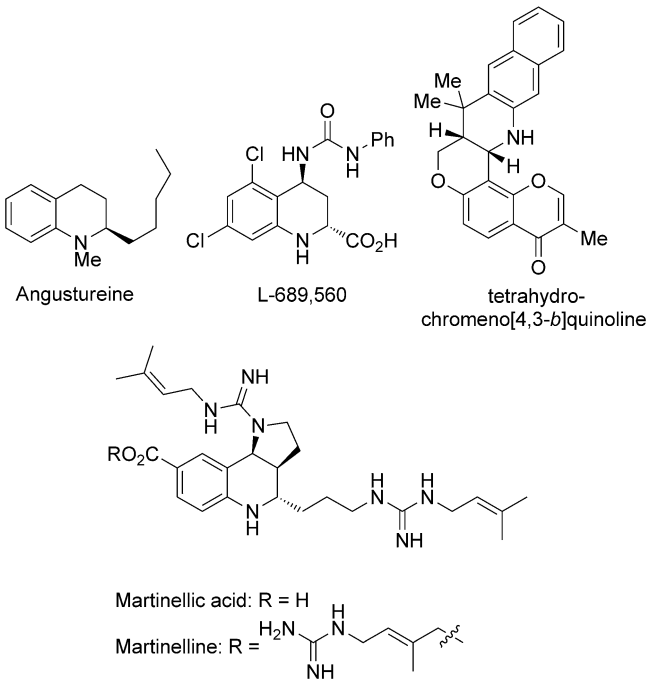
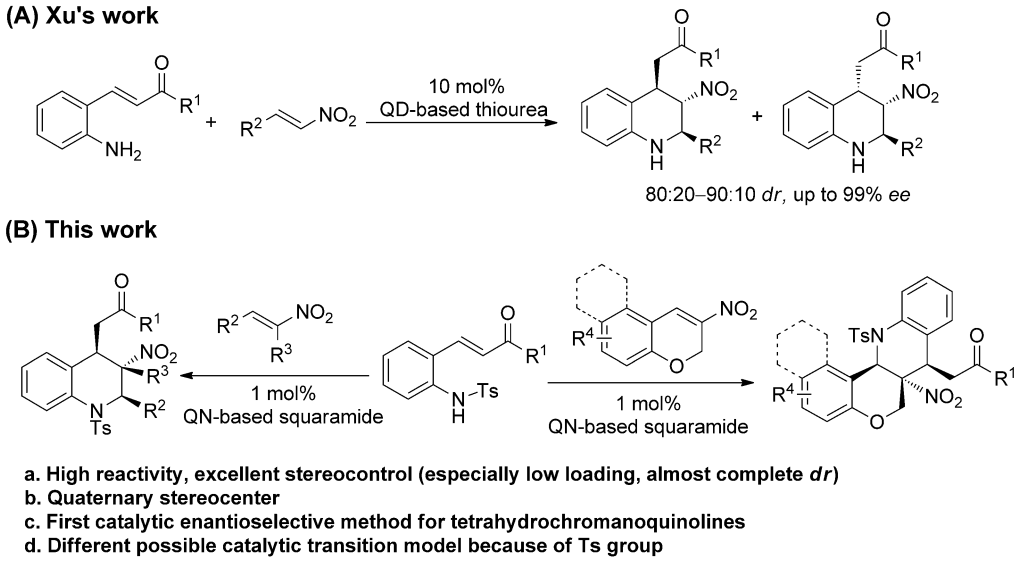


Figure 1. Examples of tetrahydroquinoline derivatives.



Scheme 1. Organocatalytic cascade aza-Michael/Michael addition for tetrahydroquinoline derivatives.

organocatalytic cascade reactions represent impressive examples.[5] Recently, Xu and co-workers successively reported chiral thiourea-catalyzed highly enantioselective cascade Michael/aza-Henry and aza-Michael/Michael reactions for the synthesis of tetrahydroquinoline derivatives with three contiguous stereocenters (Scheme 1A). In the two reports, high yields and excellent enantioselectivities were always achieved. But there were some shortcomings including relatively low reactivity, and only moderate to good diastereoselectivities in most cases. Given the limited successes, the development of efficient catalytic enantioselective methods for this important class of heterocyclic compounds is still in demand.

Organocatalytic cascade reactions have emerged as a powerful tool for the one-pot construction of multiple bonds in the modern organic synthesis.[6] As a new class of good hydrogen-bonding organocatalysts,[7] squaramides have been increasingly utilized in these cascade reactions.[8] In keeping with our interest in organocatalytic reactions using squaramide catalysts,[9] we would like to document an efficient squaramide-catalyzed highly asymmetric cascade aza-Michael/Michael addition reaction[10] for the synthesis of tetrahydroquinolines and tetrahydrochromanoquinolines (Scheme 1B).

Results and Discussion

Inspired by Xu's cascade aza-Michael/Michael strategy, we envisioned that enhanced reactivity could be achieved by employing *N*-pg-2-aminoenones instead of 2-aminoenones in the bifunctional catalytic system (where pg is a strong electron-withdrawing protecting group). This is because *N*-pg-2-aminoenones with a base catalyst could be transformed into nitrogen anion species, which display much higher nucleophilicity than arylamines. To verify the viability of this concept, we chose readily accessible 2-tosylaminochalcone **1a** and β-methyl-β-nitrostyrene **2a** as the model substrates. The utilization of β-methyl-β-nitrostyrene **2a** could lead to the formation of one quaternary stereocenter albeit with relatively low reactivity. Initially, the model reaction was performed in the presence of 5 mol% quinine-derived squaramide **I** (Figure 2) at room temperature. To our delight, the cascade aza-Michael/Michael addition was completed within 12 h and afforded the desired tetrahydroquinoline **3aa** in excellent yield with excellent diastereoselectivity and enantioselectivity (99:1 *dr*, 97% *ee*). When pg was an Ac, Boc or Cbz group, no reaction occurred. This result indicates the reaction requires sufficient acidity of the NH group. With the above excellent result in hand, we evaluated a small library of organocatalysts for this cascade process. The results are presented in Table 1. Quinine-derived squaramide **II** bearing a 4-CF_3 group on the aromatic ring gave an inferior result (Table 1, entry 2). When squaramides **III** and **IV** derived from quinidine were utilized, the opposite enantiomers of **3aa** were achieved with the same excellent stereoselectivity, albeit with lower yield for the later (Table 1, entries 3 and 4). We then turned our attention to squaramide catalysts **V** and **VI** derived from (1*S*,2*S*)-cyclohexane-1,2-diamine (Table 1, entries 5 and 6). Squaramide **VI** gave almost the same result as **I** and **III**. The C_2-symmetrical quinine-derived squaramide **VII** was also examined, but no better result was observed (Table 1, entry 7). Given the facile synthesis and cheap starting material quinine, we favored squaramide **I**. In contrast to squar amide **I**, quinine-derived thiourea **VIII** displayed significantly lower re-

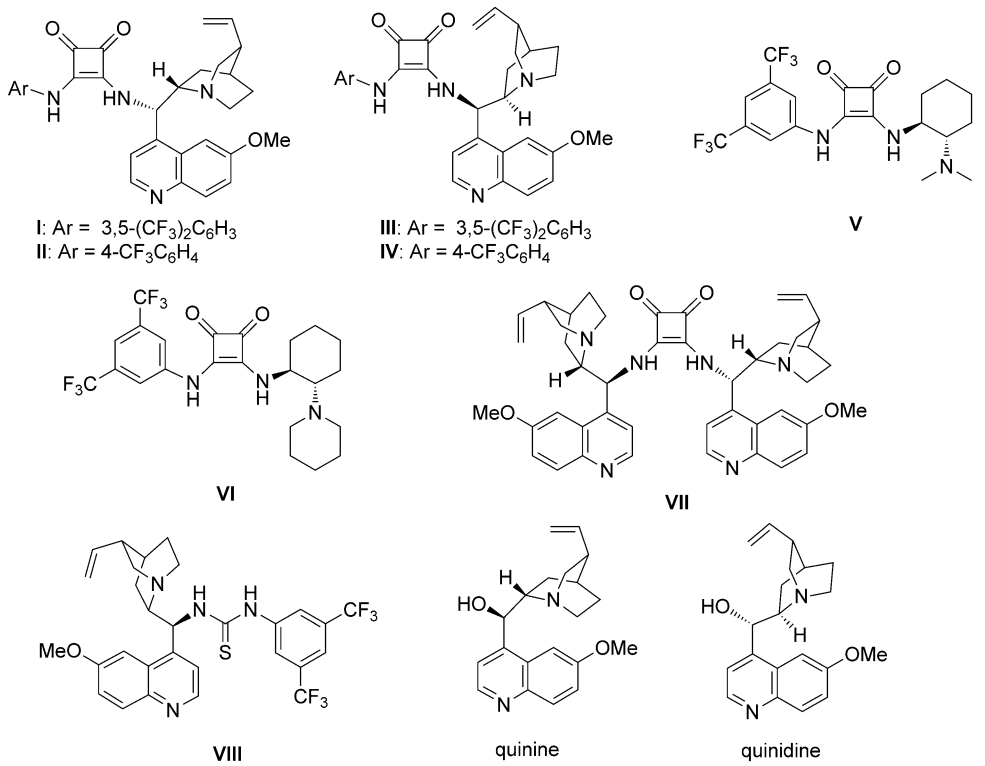
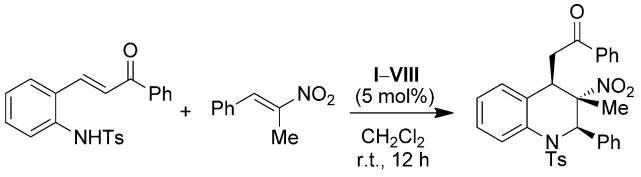


Figure 2. Structures of organocatalysts.

activity and enantioselectivity (Table 1, entry 8). In addition, quinine and quinidine were used as promoters, but very low yields and enantioselectivities were obtained (Table 1, entries 9 and 10).

Table 1. Screening of organocatalysts.[a]



1a 2a 3aa

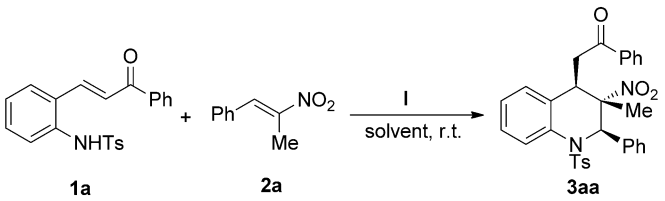
Entry	Catalyst	Yield [%][b]	*dr*[c]	*ee* [%][c]
1	**I**	97	99:1	97
2	**II**	75	96:4	95
3	**III**	95	99:1	97[d]
4	**IV**	75	99:1	97[d]
5	**V**	90	99:1	90
6	**VI**	94	99:1	97
7	**VII**	75	92:8	93
8	**VIII**	53	97:3	82
9	quinine	15	97:3	19
10	quinidine	12	95:5	17[d]

[a] *Conditions:* **1a** (0.11 mmol), **2a** (0.1 mmol), catalyst (5 mol%), and CH_2Cl_2 (0.5 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Opposite enantiomer.

With squaramide **I** as the optimal catalyst, we investigated the effect of solvent and catalyst loading for the optimal reaction conditions. The results are shown in Table 2. All screened solvents afforded excellent stereoselectivities, but only chlorinated solvents gave excellent yields (Table 2, entries 1–7). On account of the best stereoselectivity in toluene, we tried the mixtures of toluene and a chlorinated solvent (Table 2, entries 8 and 9). Compared with a single chlorinated solvent, the mixed solvent could improve the stereoselectivity slightly and accelerate the reaction. Subsequently, the effect of catalyst loading was examined. Excellent stereoselectivity was maintained with a reduced catalyst loading (2 or 1 mol%) (Table 2, entries 10 and 11). Considering the yield and reaction time, 1 mol% catalyst loading was an appropriate choice.

Having established the optimal reaction conditions, we explored the scope of the asymmetric cascade reaction for the synthesis of tetrahydroquinolines. The results are summarized in Table 3. A variety of 2-tosylaminoenones **1** was first tested. Among them, 2-tosylaminochalcones **1a–f** with different substitutions reacted smoothly with β-methyl-β-nitrostyrene **2a** to afford the corresponding products in high yields with excellent diastereoselectivities and enantioselectivities (>99:1 *dr*, 97–99% *ee*) (Table 3, entries 1–6). Steric

Table 2. Optimization of reaction conditions.[a]



1a 2a 3aa

Entry	Solvent	Loading [mol%]	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][c]
1	CH_2Cl_2	5	12	97	99:1	96.7
2	PhMe	5	12	74	>99:1	98.5
3	THF	5	12	29	99:1	96.7
4	MeCN	5	12	47	98:2	96.9
5	*i*-PrOH	5	12	41	99:1	94.7
6	DCE	5	12	96	99:1	97.3
7	$CHCl_3$	5	12	97	99:1	95.6
8	CH_2Cl_2/PhMe (1:1)	5	6	98	>99:1	97.3
9	DCE/PhMe (1:1)	5	6	99	>99:1	97.6
10	DCE/PhMe (1:1)	2	12	96	>99:1	98.1
11	DCE/PhMe (1:1)	1	24	98	>99:1	97.8

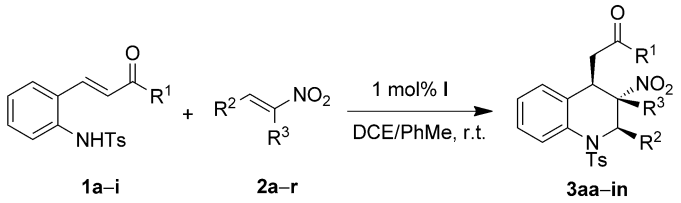
[a] *Conditions:* **1a** (0.11 mmol), **2a** (0.1 mmol), catalyst **I**, and solvent (0.5 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

hindrance of R^1 group benefits the enantioselectivity. 2-Tosylaminoenones **1g** and **1h** with aliphatic R^1 groups were viable substrates and gave 40% *ee* and 92% *ee*, respectively (Table 3, entries 7 and 8). Then we examined a wide array of different substituted α,β-disubstituted nitroalkenes **2b**–**m**. In most cases, high yields and excellent stereoselectivities were obtained (Table 3, entries 9–17). The results show that the electronic nature and position of the substituents on the aromatic rings have little influence on the cascade process. Although the substrates **2k** and **2m** displayed relatively low reactivity, comparable results were achieved by strengthening the reaction conditions (Table 3, entries 18 and 20). The alkene **2l** dramatically diminished the yield as compared to **2k**, which may be due to the electron-rich and sterically hindered nature of the cyclohexyl ring (Table 3, entry 19 *vs.* entry 18). In addition, we also examined a small library of β-substituted nitroalkenes **2n**–**r**. These substrates exhibited much higher reactivity and provided the corresponding products in excellent yields with excellent diastereoselectivities and enantioselectivities (>99:1 *dr*, 97–98% *ee*) (Table 3, entries 21–25). Pleasingly, 2-tosylaminoenoate **1i** also reacted with nitroalkene **2n** to furnish the corresponding tetrahydroquinoline **3in** with a comparable result (Table 3, entry 26). The absolute configuration of **3aa** was unambiguously established to be 2*R*,3*S*,4*R* by X-ray analysis (Figure 3),[11] and those of other products were assigned by analogy.

With the above success, we tried to extend the substrate scope to 3-nitro-2*H*-chromenes for the synthesis of tetrahydrochromanoquinolines. The reaction of 2-tosylaminochalcone **1a** and 3-nitro-2*H*-chromene **4a** was performed under the above optimal reaction conditions. Pleasingly, the reaction was completed within 3 h and provided the desired tetrahydrochromanoquinoline **5aa** in excellent yield with excellent diastereoselectivity and enantioselectivity. So we directly explored the scope of the asymmetric cascade aza-Michael/Michael addition for tetrahydrochromanoquinolines without re-optimizing the reaction conditions. The results are presented in Table 4. A range of different substituted 2-tosylaminochalcones **1a**–**f** and 3-nitro-2*H*-chromenes **4a**–**g** were tested. Different electronic and steric variations were tolerated. In almost all cases, the corresponding products were obtained in excellent yields with excellent diastereoselectivities and enantioselectivities (>99:1 *dr*, 94–99% *ee*) (Table 4, entries 1–6, 10–15). Only 3-nitro-2*H*-chromene **4h** bearing a naphthyl ring afforded 90% *ee* (Table 4, entry 16). 2-Tosylaminoenones **1g** and **1h** with aliphatic R^1 groups worked well in this cascade process (Table 4, entries 7 and 8). 2-Tosylaminoenoate **1i** was also a viable substrate and gave a comparable result in a prolonged time (Table 4, entry 9). These results show that there is not much difference in the reactivity between 3-nitro-2*H*-chromenes and β-substituted nitroalkenes in this cascade process. The absolute configuration of **5aa** was also determined to be 6a*S*,7*R*,12a*R* by X-ray analysis (Figure 4),[11] and those of other products were assigned by analogy.

As shown in Scheme 2, the further substrate scope with other cyclic nitroalkenes was investigated. When

Table 3. Scope of asymmetric cascade aza-Michael/Michael addition for tetrahydroquinolines.[a]



1a–i **2a–r** **3aa–in**

Entry	R^1	R^2	R^3	Time [h]	Product	Yield [%][b]	*dr*[c]	*ee* [%][c,d]
1	C_6H_5	C_6H_5	Me	24	**3aa**	98	>99:1	98
2	4-ClC_6H_4	C_6H_5	Me	24	**3ba**	92	>99:1	98
3	4-BrC_6H_4	C_6H_5	Me	24	**3ca**	96	>99:1	97
4	4-MeC_6H_4	C_6H_5	Me	48	**3da**	85	>99:1	99
5	4-$MeOC_6H_4$	C_6H_5	Me	48	**3ea**	89	>99:1	99
6	2-$MeOC_6H_4$	C_6H_5	Me	48	**3fa**	96	>99:1	98
7[e]	Me	C_6H_5	Me	24	**3ga**	90	99:1	40
8[e]	*t*-Bu	C_6H_5	Me	24	**3ha**	95	>99:1	92
9	C_6H_5	4-FC_6H_4	Me	24	**3ab**	97	>99:1	97
10	C_6H_5	4-ClC_6H_4	Me	24	**3ac**	94	>99:1	97
11	C_6H_5	2-ClC_6H_4	Me	24	**3ad**	95	99:1	96
12	C_6H_5	4-BrC_6H_4	Me	24	**3ae**	95	>99:1	97
13	C_6H_5	4-MeC_6H_4	Me	24	**3af**	95	>99:1	97
14	C_6H_5	4-$MeOC_6H_4$	Me	48	**3ag**	89	>99:1	97
15	C_6H_5	2-$MeOC_6H_4$	Me	48	**3ah**	89	>99:1	95
16	C_6H_5	2-furyl	Me	24	**3ai**	98	>99:1	97
17	C_6H_5	cinnamyl	Me	48	**3aj**	83	>99:1	97
18[e]	C_6H_5	*i*-Pr	Me	48	**3ak**	89	>99:1	98
19[e,f]	C_6H_5	cyclohexyl	Me	48	**3al**	49	>99:1	97
20[e,f]	C_6H_5	C_6H_5	Et	24	**3am**	92	>99:1	94
21	C_6H_5	C_6H_5	H	2	**3an**	99	>99:1	97
22	C_6H_5	4-ClC_6H_4	H	2	**3ao**	99	>99:1	97
23	C_6H_5	4-$MeOC_6H_4$	H	2	**3ap**	99	>99:1	97
24	C_6H_5	2-$MeOC_6H_4$	H	3	**3aq**	95	>99:1	97
25	C_6H_5	2-thienyl	H	2	**3ar**	97	>99:1	98
26[e]	OEt	C_6H_5	H	24	**3in**	93	>99:1	97

[a] *Conditions:* **1** (0.22 mmol), 2 (0.2 mmol), catalyst **I** (1 mol%), and DCE/PhMe (1:1, 1 mL). DCE = 1,2-dichloroethane.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Enantiomeric excess of the major diastereomer.
[e] 5 mol% of catalyst **I**.
[f] 50 °C.

1,2-dihydro-3-nitronaphthalene **4i** was used, the product **5ai** was obtained in good yield with excellent stereoselectivity. 1-Nitrocyclohexene **4j** gave comparable stereoselectivity, but showed very low reactivity.

To highlight the synthetic value of this methodology, the gram-scale preparations of **3aa** and **5aa**, and synthetic transformation were described. The cascade reactions of **1a** and **2a** or **4a** on a gram scale were performed well in the presence of 0.5 mol% **I** without any significant changes in yield or stereoselectivity (Scheme 3). Tetrahydrochromanoquinoline **5aa** was easily converted into amine **6** by Pd/C-catalyzed hydrogenation; its structure was also determined by X-ray analysis.[11] Tetrahydrochromanoquinoline **5ia** was readily transformed into γ-lactam **7** in good yield with the excellent stereoselectivity being retained by two simple steps (Scheme 4).

We found that the catalytic model proposed by Xu's group could not explain our observed stereochemical result.[5b] The configurations of products deduced following Xu's model are opposite to those determined by X-ray analysis. After reconfirming that the X-ray crystal structures of **3aa**, **5aa**, and **6** were correct, we thought that the introduction of a Ts group could change the model. On the basis of the absolute configuration of **3aa**, a different possible transition state model was proposed for this cascade process (Figure 5). 2-Tosylaminochalcone **1a** is deprotonated by the basic nitrogen atom of the quinine moiety, and its sulfonamide moiety is coordinated to the squaramide one. Meanwhile, nitroalkene **2a** is ori-

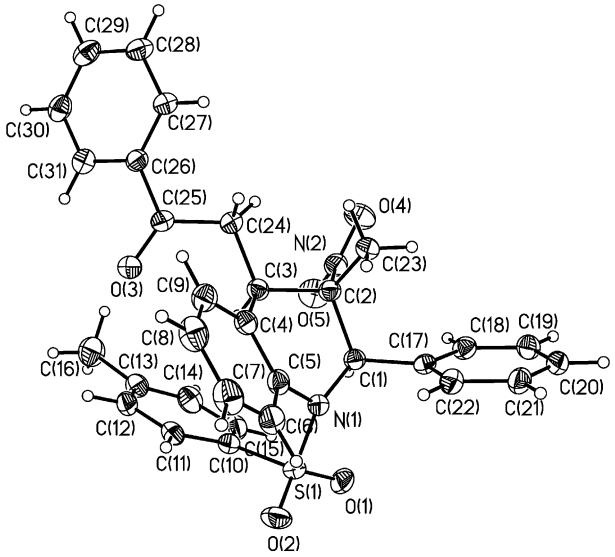


Figure 3. X-ray crystal structure of **3aa**.

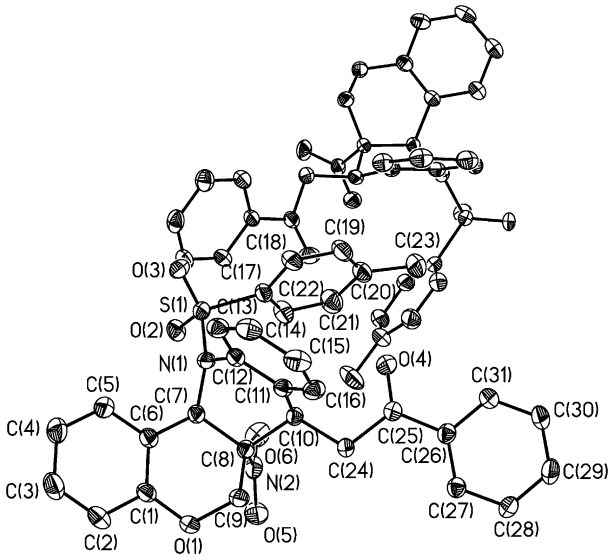
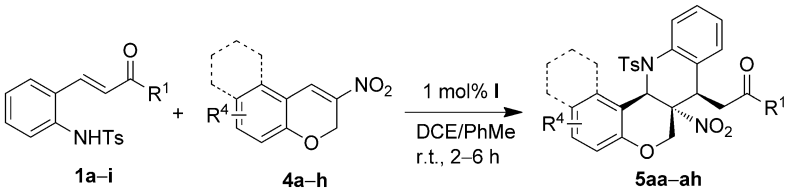


Figure 4. X-ray crystal structure of **5aa** (hydrogen atoms are omitted for clarity).

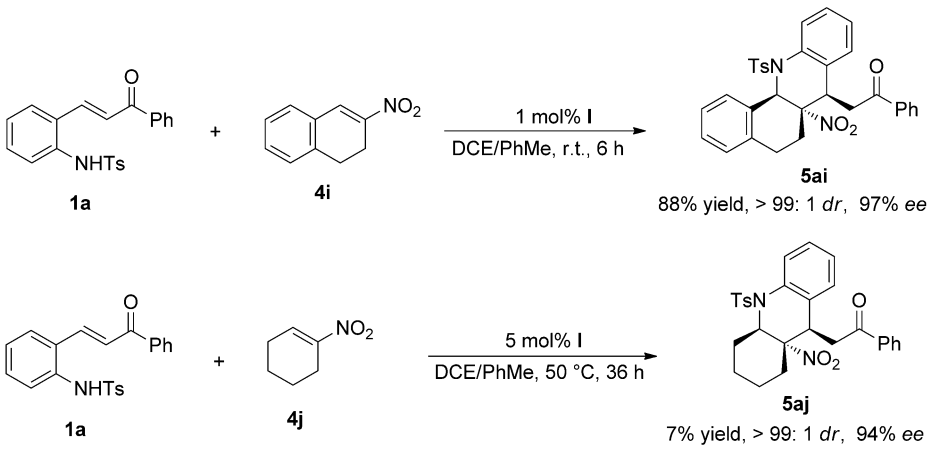
ented and activated by the quinine moiety through hydrogen bonding. The intermolecular aza-Michael addition first gives *R*-configured intermediate through the *Re* face attack. Then the intermediate could undergo intramolecular Michael addition through the *Re* face attack, forming the 2*R*,3*S*,4*R*-configured product **3aa**.

Table 4. Scope of asymmetric cascade aza-Michael/Michael addition for tetrahydrochromanoquinolines.[a]

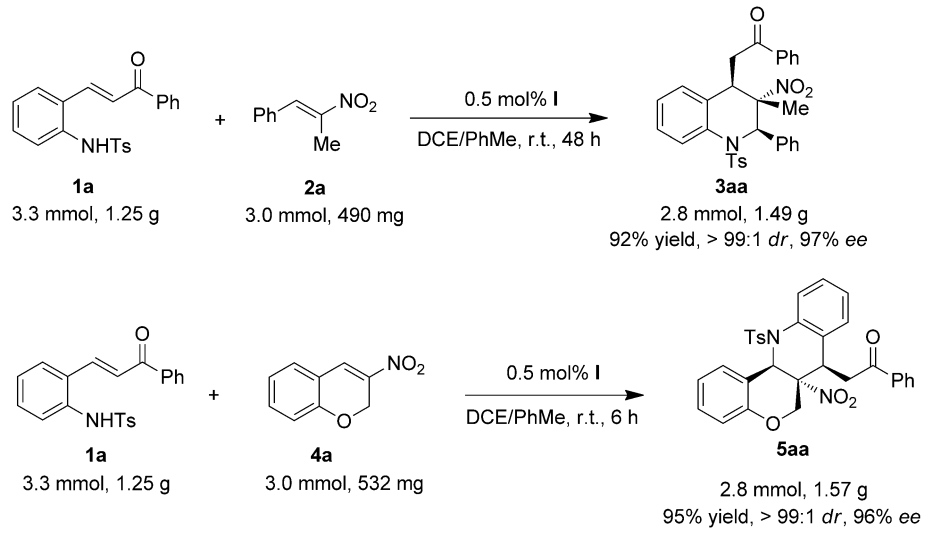


Entry	R^1	R^4	Product	Yield [%][b]	*dr*[c]	*ee* [%][c,d]
1	C_6H_5	H	**5aa**	98	>99:1	97
2	4-ClC_6H_4	H	**5ba**	98	>99:1	97
3	4-BrC_6H_4	H	**5ca**	99	>99:1	98
4	4-MeC_6H_4	H	**5da**	98	>99:1	99
5	4-MeOC_6H_4	H	**5ea**	91	>99:1	97
6	2-MeOC_6H_4	H	**5fa**	99	>99:1	97
7[e]	Me	H	**5ga**	98	>99:1	88
8[e]	*t*-Bu	H	**5ha**	98	>99:1	99
9[e,f]	EtO	H	**5ia**	90	>99:1	99
10	C_6H_5	6-Cl	**5ab**	98	>99:1	96
11	C_6H_5	6-Br	**5ac**	97	>99:1	98
12	C_6H_5	6,8-Cl_2	**5ad**	97	>99:1	96
13	C_6H_5	6,8-Br_2	**5ae**	97	>99:1	94
14	C_6H_5	8-OMe	**5af**	99	>99:1	99
15	C_6H_5	8-OEt	**5ag**	98	>99:1	97
16	C_6H_5	benzo	**5ah**	97	>99:1	90

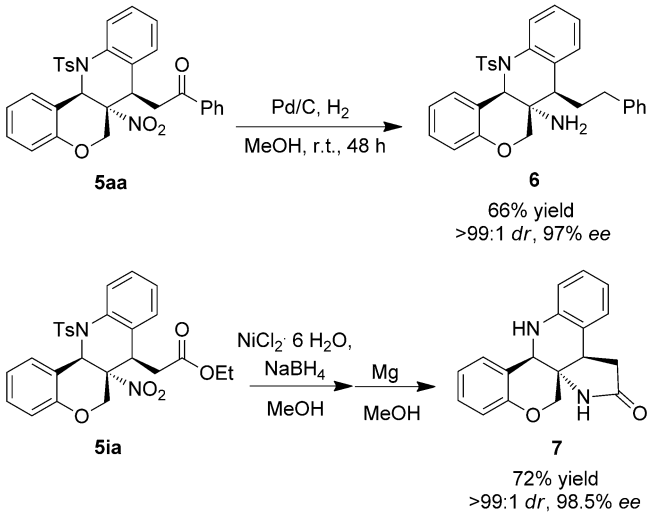
[a] *Conditions:* **1** (0.22 mmol), **4** (0.2 mmol), catalyst **I** (1 mol%), and DCE/PhMe (1:1, 1 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Enantiomeric excess of the major diastereomer.
[e] 5 mol% of catalyst **I**.
[f] Reaction for 48 h.



Scheme 2. Further investigation of substrate scope.



Scheme 3. The gram-scale preparation.



Scheme 4. The synthetic transformation of products.

Conclusions

In conclusion, we have developed an efficient highly asymmetric cascade aza-Michael/Michael reaction catalyzed by a chiral bifunctional tertiary amine-squaramide catalyst for the synthesis of tetrahydroquinolines and tetrahydrochromanoquinolines. This cascade reaction proceeded well at low catalyst loading (1 mol%) with a broad scope of substrates under mild conditions, and afforded the corresponding adducts in excellent yields with excellent diastereoselectivities and enantioselectivities (up to >99:1 *dr*, 99% *ee*). Importantly, it is the first catalytic asymmetric method for chiral tetrahydrochromanoquinolines. This protocol provides an easy and straightforward entry to highly functionalized chiral tetrahydroquinoline and tetrahydrochromanoquinoline derivatives with three

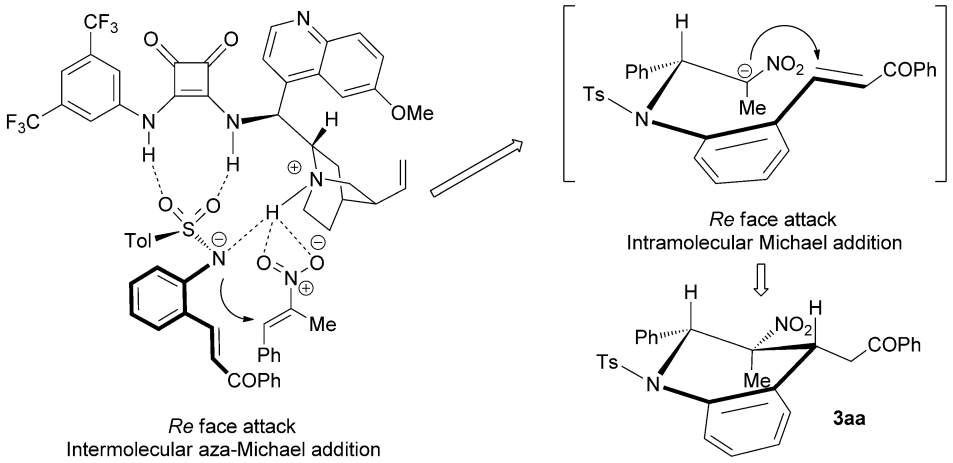


Figure 5. Proposed transition state model.

contiguous stereocenters including one quaternary center from simple starting materials.

Experimental Section

Typical Procedure for Asymmetric Cascade Aza-Michael/Michael Addition for Tetrahydroquinoline Derivative 3aa

A mixture of nitroalkene **2a** (32.6 mg, 0.2 mmol) and catalyst **I** (1.3 mg, 0.002 mmol, 1 mol%) in DCE/toluene (1:1, 1 mL) was stirred at room temperature for 10 min. Then **1a** (83.0 mg, 0.22 mmol) was added in one portion. After stirring for 24 h, the reaction mixture was concentrated and directly purified by silica gel column chromatography to afford the product **3aa** as a white solid; yield: 105.7 mg (98%); mp 215–216 °C. The diastereoselectivity and enantioselectivity were determined by HPLC (Daicel Chiralpak column IA, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL min^{-1}, detection at 254 nm): t_{minor} = 9.7 min, t_{major} = 11.0 min, 98% *ee*, >99:1 *dr*; $[\alpha]_D^{20}$: −27.3 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 7.2 Hz, 2H), 7.62–7.55 (m, 3H), 7.49–7.41 (m, 3H), 7.34–7.29 (m, 5H), 7.20–7.14 (m, 3H), 6.69 (d, J = 7.6 Hz, 1H), 6.26 (s, 1H), 3.37–3.24 (m, 2H), 2.51 (d, J = 16.8 Hz, 1H), 2.43 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 144.8, 138.5, 135.9, 135.8, 134.3, 133.6, 133.1, 130.0, 128.8, 128.7, 128.3, 128.2, 127.9, 127.3, 127.1, 126.6, 125.2, 109.7, 98.2, 67.5, 40.8, 34.8, 21.7, 16.4; IR (KBr): ν = 3065, 3039, 2922, 1691, 1597, 1543, 1487, 1453, 1356, 1242, 1356, 1242, 1168, 1083, 1061, 981, 926, 808, 756, 700, 689, 663, 652, 570, 535 cm^{-1}; HR-MS (ESI): m/z = 558.20581, calcd. for $C_{31}H_{32}N_3O_5S$ $[M+NH_4]^+$: 558.20572.

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