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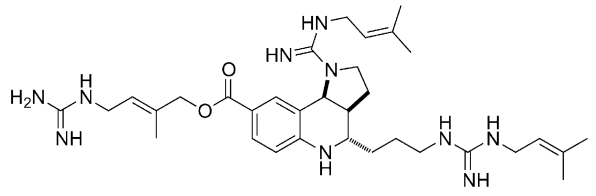
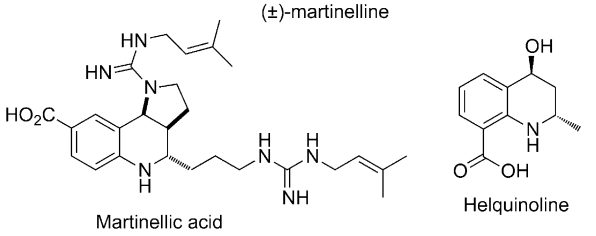
Organocatalytic Aza-Michael–Michael Cascade Reactions: A Flexible Approach to 2,3,4-Trisubstituted Tetrahydroquinolines

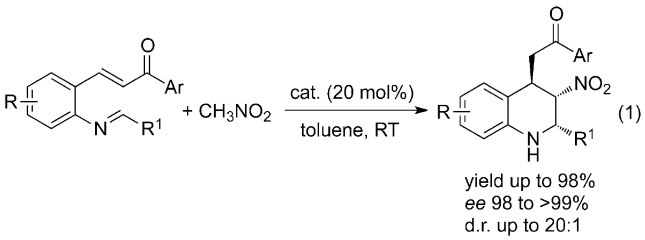
Zhen-Xin Jia,[a] Yong-Chun Luo,[a] Yao Wang,[a] Liang Chen,[a] Peng-Fei Xu,*[a] and Binghe Wang[b]

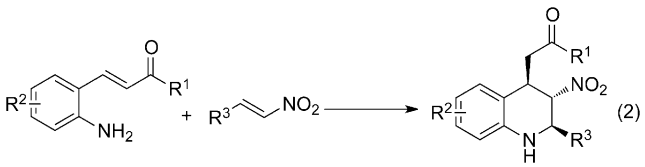
Tetrahydroquinoline derivatives are an important class of heterocycles and the tetrahydroquinoline ring system occurs in various natural products and pharmaceuticals.[1] Hundreds of tetrahydroquinolines containing various simple or complex substituents have been used as pharmaceutical agents, pesticides, antioxidants, corrosion inhibitors, and so forth.[2] For example, martinellic acid and martinelline, which are found in Amazonian lowland rainforests, display modest antibiotic activity and micromolar binding affinity to G-protein coupled receptors (GPCR).[3] Additionally, helquinoline, which is found in Janibacter limosus, is now used as a tetrahydroquinoline-based antibiotic.[4] Therefore, there is significant interest in developing methods for the synthesis of tetrahydroquinoline derivatives with careful stereochemical control.[5] For this reason, we became interested in the controlled synthesis of diastereoisomers of tetrahydroquinoline derivatives.





Organocatalytic cascade/domino reactions have become a powerful synthetic paradigm for the construction of multiple carbon–carbon or carbon–heteroatom bonds in a single operation.[6] Recently, we communicated a new method for the two-component, two-step synthesis of polysubstituted tetrahydroquinoline derivatives through an organocatalytic asymmetric tandem Michael addition and aza-Henry reaction [Eq. (1)].[7] This type of reaction yields the *cis*-isomer at the 2,3-positions. In our effort to further explore the synthesis of quinolones with diverse structural features, we report, herein, a new method that provides products in a single operation by using two components through a cascade aza-Michael–Michael reaction [Eq. (2)].[8] As a result, *trans*-isomers at the 2,3-positions are obtained as the major products. Significantly, the stereochemical control is different from that of the tandem Michael addition–aza-Henry reaction and thus allows for the preparation of substituted tetrahydroquinolines with diverse stereochemical features.





Our investigation began with the reaction of (*E*)-3-(2-aminophenyl)-1-phenylprop-2-en-1-one (**1a**) with (*E*)-1-chloro-2-(2-nitrovinyl)benzene (**2a**) catalyzed by quinine thiourea derivative **A** (20 mol%) in toluene at room temperature. To our delight, the corresponding product **3a** was formed in 95% yield with high enantioselectivity (95% *ee*), albeit in low diastereoselectivity (d.r. 67:33; Table 1, entry 1). Next,

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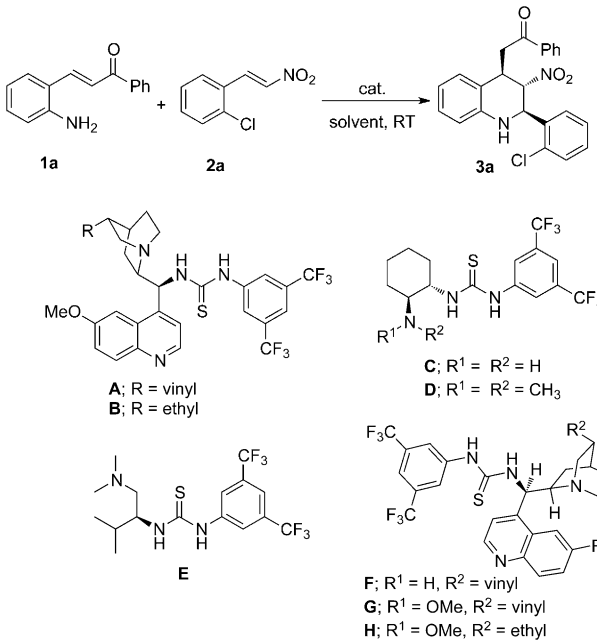
Table 1. Screening of the reaction conditions.[a]



Entry	Catalyst	Solvent	Time [h][b]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**A**	toluene	72	95	67:33	95
2	**B**	toluene	72	95	67:33	96
3	**C**	toluene	18	94	80:20	75
4	**D**	toluene	96	88	50:50	77
5	**E**	toluene	96	80	67:33	67
6	**F**	toluene	72	96	75:25	96
7	**G**	toluene	48	96	83:17	98
8	**H**	toluene	48	93	83:17	98
9	**G**	Et_2O	48	94	80:20	94
10	**G**	xylene	48	87	67:33	90
11	**G**	CH_2Cl_2	60	90	67:33	82
12	**G**	THF	84	74	67:33	81
13	**G**	CHCl3	60	92	67:33	79
14	**G**	CH_3CN	72	86	50:50	86
15[f]	**G**	toluene	60	93	83:17	98

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol), and the organocatalyst (20 mol%) in the indicated solvent (1.0 mL) at room temperature. [b] Reaction time was determined by TLC. [c] Combined yields of the diastereomers after flash column chromatography. [d] Determined by ^{1}H NMR analysis of the crude products. [e] Refers to major compound **3a**; determined by chiral-phase HPLC analysis (AD-H column). [f] The reaction was carried out with 10 mol% catalyst.

several catalysts were screened for this reaction (Table 1, entries 2–8). It was found that all of these catalysts catalyzed the reaction to provide the desired product. Among these catalysts, chiral bifunctional tertiary amine thioureas **G** and **H** gave the best diastereoselectivity (d.r. 83:17) and enantioselectivity (98% *ee*). We then studied the effect of the solvent on the reaction and tested a variety of polar and nonpolar solvents (Table 1, entries 9–14). In summary, the reactions in less polar solvents, such as toluene, CH_2Cl_2, Et_2O, and THF, generally proceeded with relatively high yield and enantioselectivity. If the catalyst loading was further reduced from 20 to 10 mol%, it did not influence the yield or enantioselectivity (Table 1, entry 15 vs. entry 7). Therefore, the optimal conditions were found to be the use of 10 mol% of catalyst **G** in toluene at room temperature.

Based on the established optimal reaction conditions, we explored the scope of the cascade aza-Michael–Michael process by using a variety of *ortho*-amino-substituted α,β-unsaturated ketones and nitroalkenes in toluene at room temperature (Table 2). In most cases, it was found that the reactions provided the corresponding products with excellent yields and enantioselectivities. R^1 groups containing a variety of substituents on the aromatic ring, including electron-donating (Table 2, entries 2–5) and electron-withdrawing (Table 2, entries 6–9) groups could efficiently participate in this reaction. However, the reaction proceeded faster with substrates containing electron-donating substituents than with those containing electron-withdrawing substituents (Table 2, entries 2 to 5 vs. entries 6 to 9). This observation could be attributed to the higher nucleophilic activity of aromatic amines containing α,β-unsaturated ketones with electron-donating substituents than those with electron-withdrawing substituents. A heteroaromatic group could also be employed to provide the product with excellent enantioselectivity (Table 2, entry 10). Furthermore, substituted anilines were also suitable for this cascade process (Table 2, entries 11–13). In this cascade reaction, diastereomers formed from *ortho*-halogen-substituted nitroalkenes could be isolated by flash column chromatography (Table 2, entries 1–17, 19, and 20), but diastereomers formed from other types of nitroalkene, including *meta*- and *para*-halogen-substituted nitroalkenes and *ortho*-substituted, nonhalogenated nitroalkenes only show one spot in TLC, which means that they could not be isolated by column chromatography (Table 2, entry 18). Noticeably, aliphatic α,β-unsaturated ketones proceeded smoothly to provide the desired products in good yields, albeit with moderate enantioselectivities (Table 2, entries 19 and 20). Furthermore, the reaction of a nitroalkene containing an alkyl group, such as cyclohexyl, gives the corresponding product with high yield and excellent enantioselectivity (Table 2, entry 21).

To determine the absolute configuration of the cascade reaction product, the X-ray crystal structure of compound **3o**, containing a bromine atom, was obtained (Figure 1).[9] As shown in Figure 1, the newly formed stereogenic centers in **3o** were confirmed to be 2*R*,3*S*,4*R*. Similarly, the absolute

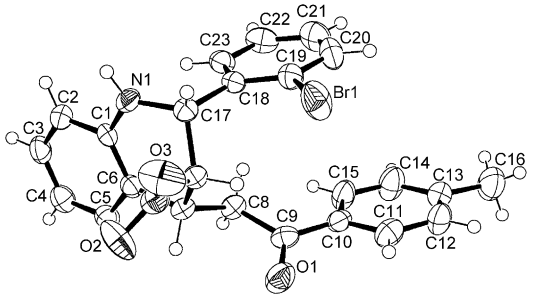
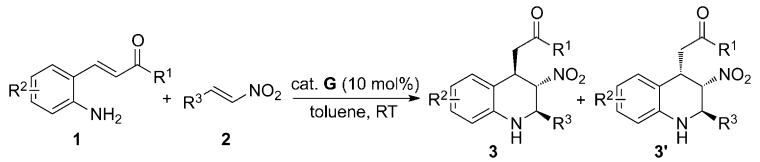


Figure 1. The X-ray crystal structure of the compound **3o**.

Table 2. The cascade aza-Michael–Michael reactions of *ortho*-amino-substituted α,β-unsaturated ketones **1** and nitroalkenes **2**.[a]



Entry	R^1	R^2	R^3	Product	Time [h][b]	Yield [%][c]	d.r.[d]	*ee* **3**/**3′** [%][e]
1	Ph	H	2-ClC_6H_4	**3a**/**3a′**	60	93	83:17	98/97
2	4-$CH_3C_6H_4$	H	2-ClC_6H_4	**3b**/**3b′**	48	92	83:17	98/98
3	4-$OCH_3C_6H_4$	H	2-ClC_6H_4	**3c**/**3c′**	48	95	83:17	99/99
4	3-$OCH_3C_6H_4$	H	2-ClC_6H_4	**3d**/**3d′**	48	95	83:17	97/98
5	2-$OCH_3C_6H_4$	H	2-ClC_6H_4	**3e**/**3e′**	48	92	83:17	81/88
6	4-ClC_6H_4	H	2-ClC_6H_4	**3f**/**3f′**	72	90	80:20	98/99
7	4-BrC_6H_4	H	2-ClC_6H_4	**3g**/**3g′**	72	93	83:17	99/99
8	3-BrC_6H_4	H	2-ClC_6H_4	**3h**/**3h′**	72	90	80:20	97/98
9	2-FC_6H_4	H	2-ClC_6H_4	**3i**/**3i′**	72	91	86:14	95/96
10	2-furyl	H	2-ClC_6H_4	**3j**/**3j′**	60	91	80:20	93/98
11	Ph	4-Cl	2-ClC_6H_4	**3k**/**3k′**	72	90	86:14	97/97
12	Ph	5-Cl	2-ClC_6H_4	**3l**/**3l′**	72	91	83:17	98/96
13	Ph	5-OMe	2-ClC_6H_4	**3m**/**3m′**	48	93	86:14	96/98
14	Ph	H	2-BrC_6H_4	**3n**/**3n′**	60	95	86:14	98/98
15	4-$CH_3C_6H_4$	H	2-BrC_6H_4	**3o**/**3o′**	48	96	83:17	98/99
16	Ph	H	2-FC_6H_4	**3p**/**3p′**	60	94	86:14	98/98
17	Ph	H	2,4-$Cl_2C_6H_4$	**3q**/**3q′**	60	97	86:14	98/95
18	Ph	H	Ph	**3r**/**3r′**	60	96	86:14	99/93
19	CH_3	H	2-ClC_6H_4	**3s**/**3s′**	48	90	80:20	35/73
20	*i*Pr	H	2-ClC_6H_4	**3t**/**3t′**	48	92	80:20	55/88
21	Ph	H	cyclohexyl	**3u**/**3u′**	72	91	90:10	97/94

[a] All reactions were carried out with **1** (0.1 mmol), **2** (0.12 mmol), and organocatalyst **G** (10 mol%) in toluene (1.0 mL) at room temperature. [b] Reaction time was determined by TLC. [c] Combined yields of each of the diastereomers after flash column chromatography. [d] Determined by ^{1}H NMR analysis of the crude products. [e] Determined by chiral-phase HPLC analysis (AD and AS column).

configuration of the minor diastereoisomer **3o′** was confirmed to be 2*R*,3*S*,4*S* by X-ray crystallographic analysis (see the Supporting Information).[9]

The model of the cascade reaction was proposed to be through a dual activation process by the chiral bifunctional thiourea catalyst.[10] The catalyst **G** activates the nitroalkene through multiple hydrogen-bonding interactions while its basic tertiary amine site activates the nucleophilic aniline (Figure 2). The R^1 (aromatic group) is part of a large conjugate system, all carbon atoms are in the same plane. As a result, the enantioselectivity of reactions with aliphatic R^1 groups is lower than for aromatic ones.

Since ring-fused tetrahydroquinoline derivatives have potential biological activities,[11] we performed a simple transformation of product **3a** to form **4a**. The ring-fused core was successfully produced by reductive amination in high yield (89%), diastereoselectivity (83:17), and enantioselectivity (97% *ee*; Scheme 1). In this transformation, a new chiral center was generated and the configurations of the other three chiral carbon atoms were retained. The configuration of the product **4a** was determined by an nOe experiment.

In summary, we have developed a new method for the enantioselective synthesis of polysubstituted tetrahydroquinolines through cascade aza-Michael–Michael addition reactions, in which *ortho*-amino-substituted α,β-unsaturated ketones and nitroalkenes are employed as the starting materials. This cascade process provides the tetrahydroquinoline derivatives with excellent yields (90–97%), good diastereoselectivity (up to 90:10), and generally high enantioselectivity (up to 99% *ee*), and these products can be easily transformed into various ring-fused tetrahydroquinolines. Moreover, the method described herein provides an important complement to the synthesis of chiral polysubstituted tetrahydroquinolines and would be beneficial to the further study and discovery of new biologically active compounds of this kind.

Experimental Section

General procedure: (*E*)-1-Chloro-2-(2-nitrovinyl)benzene (**2a**; 22.0 mg, 0.12 mmol) was added to a mixture of (*E*)-3-(2-aminophenyl)-1-phenylprop-2-en-1-one (**1a**; 22.3 mg, 0.1 mmol) and the chiral bifunctional thiourea catalyst (6.0 mg, 0.01 mmol) in toluene (1.0 mL) at room temperature. The reaction was stirred at room temperature until **1a** was completely consumed, as shown by TLC. The reaction mixture was concentrated in vacuo and purified by flash column

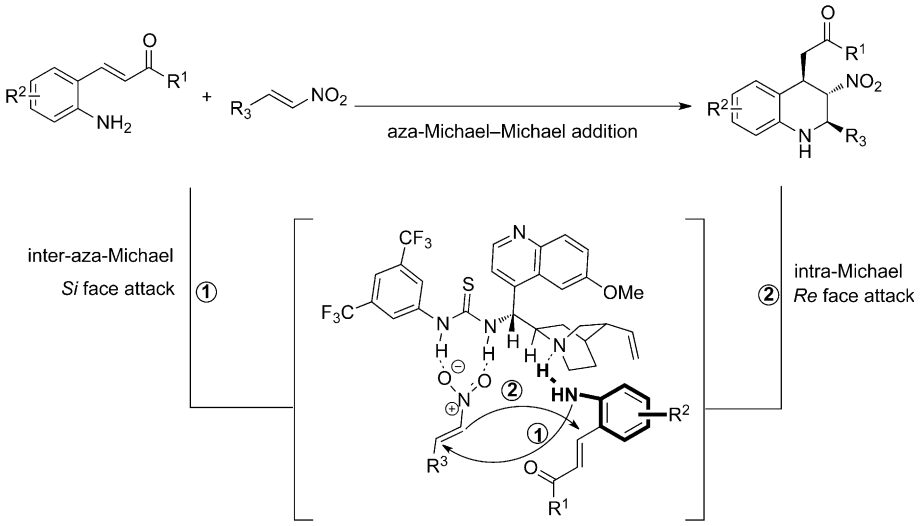
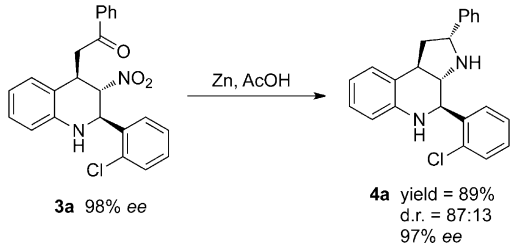


Figure 2. Proposed reaction pathway for the cascade sequence.



3a 98% *ee*

4a yield = 89%
d.r. = 87:13
97% *ee*

Scheme 1. Synthesis of the ring-fused core **4a**.

chromatography (petroleum ether/ethyl acetate = 8:1) to give **3a**/**3a′** (39.0 mg, 93%)

Acknowledgements

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Keywords: aza-Michael addition · domino reactions · Michael addition · organocatalysis · tetrahydroquinolines

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