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Asymmetric Organocatalytic Cascade Michael/Michael/Henry Reaction Sequence: Control of All Stereocenters in One Cyclohexane Skeleton

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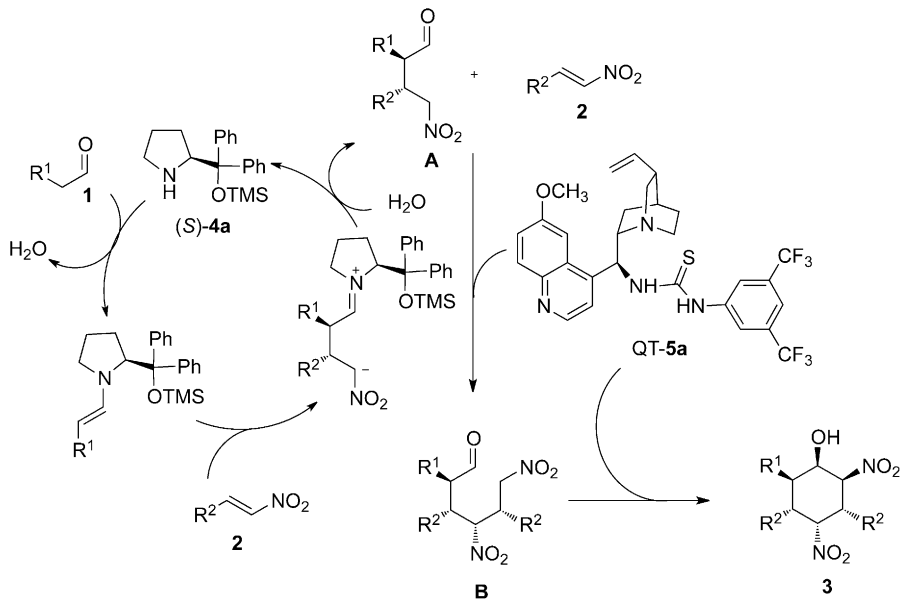
Abstract: The highly diastereo- and enantioselective relay cascade Michael/Michael/Henry reaction catalyzed by combination of readily available diphenylprolinol silyl ether and the quinine thiourea in a one-pot fashion has been developed. Up to 70% yield and up to >99% enantioselectivity of the single major isomer were obtained from the cascade reactions.

Keywords: asymmetric catalysis; cyclohexanes; domino reactions; Henry reaction; Michael addition

Asymmetric synthesis of complex molecules with control of multiple stereocenters in a one-pot fashion by asymmetric catalysis is very useful for the preparation of natural products and other molecules of interest.[1] Asymmetric organocatalytic tandem or cascade reactions are a very powerful way for achieving this goal.[2] Polysubstituted chiral cyclohexanes constructed through organocatalytic cascade approaches have attracted a great deal of attention, owing to the prevalence of such building blocks in pharmaceutical compounds and complex natural products.[3] Up to five new contiguous stereocenters in one reaction have been made by the Jørgensen group.[3f] Recently, the relay catalysis has been reported as an efficient route in asymmetric catalysis by combination of two organocatalysts or metal/organocatalyst in one-pot reactions.[4] Xu and Dixon et al. reported an excellent asymmetric organocatalytic relay cascade reaction for the synthesis of substituted cyclohexanes with four stereocenters by using two different kinds of catalysts.[4d] The synthesis of hexasubstituted cyclohexane with control of all six stereocenters by asymmetric tandem or cascade reaction still remains a challenge. To the best of our knowledge, the generation of six contiguous stereocenters in one cyclohexane skeleton from two simple compounds by an asymmetric domino reaction has been merely reported.[5] Herein we described an example of such a reaction catalyzed by the combination of two different organocatalysts in one-pot.[6]

Our proposed three-step asymmetric organocatalytic relay cascade to hexasubstituted cyclohexanes is shown in Scheme 1. In the first step, the catalyst (*S*)-**4a** activates aldehyde **1** by enamine formation, which then adds to the nitroalkene **2** in a Michael-type reaction.[7] The following hydrolysis liberates the catalyst (*S*)-**4a** and provides adduct **A**. In the subsequent step, the bifunctional base/Brønsted acid catalyst of the type QT-**5a** would activate the adduct **A** and the nitroalkene **2** again, thus promoting a second stereoselective Michael addition.[8] The Michael adduct **B**, with its suitably positioned aldehyde and nitroalkane functionalities, would then undergo a base-promoted Henry reaction to generate the desired cyclohexane **3**. As a result, three new bonds and six contiguous stereogenic centers could be assembled, incorporating multiple functional groups in a simple-to-perform, single-operation cascade sequence. In the course of the reaction, nitroalkene **2** is employed twice, which means at least two equivalents of nitroalkene are required to complete the transformation.

We initiated our investigation by using propanal **1a** and nitroalkene **2a** as the substrates combined with two catalysts, (*R*)-**4a** (10 mol%) and QT-**5a** (20 mol%). To our delight, by performing the reaction in toluene, we were able to isolate the desired product



Scheme 1. Organocascade Michael/Michael/Henry reaction promoted by a combination of two organocatalysts.

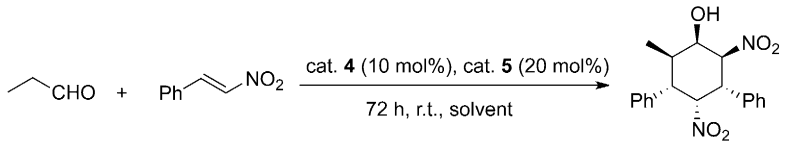
and another two minor isomers in 22% yield (Table 1, entry 1). In order to improve the yield, various catalyst combinations and different solvents were screened. Compared to (*R*)-**4a**, the combinations of (*S*)-**4a** and QT-**5a** improved the yield and the enantioselectivity of the product effectively, however the opposite enantiomer **3a** was formed (Table 1, entry 2). These results indicated that (*S*)-**4a** and QT-**5a** were matched catalyst pairs. (*S*)-**4b** and (*S*)-**4c** gave poor results (Table 1, entries 3 and 4). With (*S*)-**4a** as the first catalyst, both **5b** and **5c** showed inferior performance than QT-**5a**, indicating that QT-**5a** has an excellent asymmetric induction ability and catalytic activity (Table 1, entries 5 and 6). The combination of (*R*)-**4a** and **5c** led to the formation of the opposite enantiomer of **3a** (Table 1, entry 7). The highest yields were obtained using toluene as the solvent (Table 1, entries 2, 8, and 9).

After optimizing the reaction conditions, we studied the possibility of using different aldehydes as well as different nitroalkenes to synthesize various hexasubstituted cyclohexane derivatives. As shown in Table 2, linear aliphatic aldehydes **1a**, **1b**, **1c** could be used as the nucleophiles in reaction with nitrostyrene giving high diastereoselectivities. In all cases, the major isomers were isolated in moderate to good yields with excellent enantioselectivities (Table 2, entries 1–3).

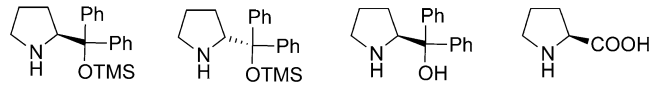
Other nitroalkenes were also examined under our standard conditions. Aromatic and heteroaromatic substituted electrophiles **2b–j** could be used well in this reaction (Table 2, entries 4–15). Excellent enantioselectivities (up to 99%) were observed, irrespective of the electronic nature or position of the substituents on the phenyl ring. Furthermore, two thiophenyl-substituted electrophiles **2i** and **2j** were also shown to be compatible in the reaction and provided the corresponding cyclohexanol derivatives **3n** and **3o** with moderate yields, good diastereoselectivities and excellent enantioselectivities (Table 2, entries 14 and 15). When we use aliphatic nitroalkenes **2**, only traces of the cyclohexane **3** can be obtained. We treated the major diastereoisomer **3a** with DBU (1 equiv.) at room temperature. After 48 h, we determined the product by ^{1}H NMR, and found that only small amounts of the minor diastereoisomer were observed (4:1:0 *dr*). In addition, we also stopped the reaction after 24 h, and checked the diastereomer ratio (13:4:1 *dr*) at that stage, which has no pronounced change compared to the result after 72 h. Furthermore, the final product **3a** which was precipitated when purification of the reaction mixture by flash chromatography was performed at room temperature, no other diastereoisomers were observed even after a few months. So the major final product must then be the thermodynamic product.

To study the mechanism of the reaction, we conducted a series of control experiments (Scheme 2). Initially, reactions were carried out using **1a** and **2a** in the presence of either (*S*)-**4a** or QT-**5a** as catalyst. However, the product **3a** was not detected when either catalyst was used. The adduct **6** was afforded by the Michael reaction of propanal (**1a**) and (*E*)-nitrostyrene (**2a**) in the presence of (*S*)-**4a** overnight in good yield (97%, the yield given is for the two isolated stereoisomers) with low diastereoselectivity (*syn*/anti = 3:1) but with high enantioselectivity (96%/92%).[7] The low diastereoselectivity was due to isomerization before **6** underwent the next step. Having obtained the pure adduct **6**, we next examined the second stage of the cascade reaction. We conducted

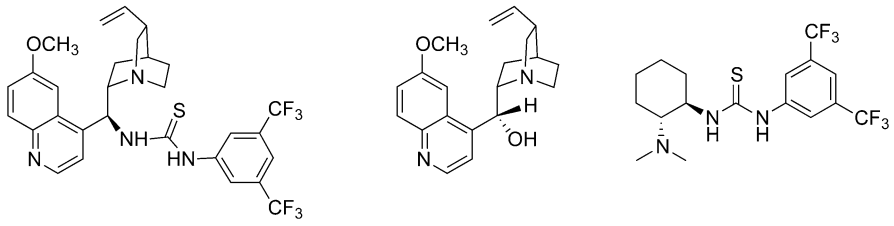
Table 1. Representative screening results for the reaction of the reaction propanal **1a** with nitroalkene **2a** by using different catalyst combinations.[a]



1a **2a** **3a**



(*S*)-**4a** (*R*)-**4a** (*S*)-**4b** (*S*)-**4c**



QT-**5a** **5b** **5c**

Entry	Cat.**4**/Cat.**5**	Solvent	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	(*R*)-**4a**/QT-**5a**	toluene	22	4:1:1	−40
2	(*S*)-**4a**/QT-**5a**	toluene	60	15:4:1	>99
3	(*S*)-**4b**/QT-**5a**	toluene	21	9:1:1	95
4	(*S*)-**4c**/QT-**5a**	toluene	52	14:4:1	99
5	(*S*)-**4a**/**5b**	toluene	27	6:1:1	88
6	(*S*)-**4a**/**5c**	toluene	39	7:1:1	63
7	(*R*)-**4a**/**5c**	toluene	61	17:5:1	−93
8	(*S*)-**4a**/QT-**5a**	CH_2Cl_2	42	9:3:1	99
9	(*S*)-**4a**/QT-**5a**	THF	29	16:4:1	99

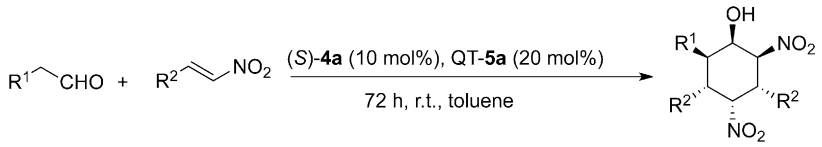
[a] The reaction was carried out with propanal **1a** (0.5 mmol), nitroalkene **2a** (1.5 mmol), catalyst **4** (10 mol%), catalyst **5** (20 mol%) in solvent (1.0 mL) at room temperature for 72 h.
[b] Combined yield of the three stereoisomers.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] The *ee* values for the isolated major product were determined by HPLC on a chiral stationary phase.

several reactions of **6** with **2a** (2 equiv.) in the presence of one or more catalysts. After 24 h, **3a** was not formed when **6** reacted with (*S*)-**4a** (Scheme 2, path A). The presence of QT-**5a** (20 mol%) led to the formation of **3a** in good diastereoselectivity (4:1:1 *dr*) and excellent enantioselectivity (>99% *ee*) and in 27% yield (the yield given is for the major isolated stereoisomer **3a**) with respect to adduct **6** (Scheme 2, path B, 24 h). Actually, the final base-promoted intramolecular Henry reaction was so quick that intermediate **7** could not be detected in either pathway. In the presence of (*S*)-**4a** (10 mol%) and QT-**5a** (20 mol%), similar results were obtained (Scheme 2, path C, 24 h). This indicated that the effect of both organocatalysts may be relatively independent.

The absolute configuration of the major stereoisomer was assigned by single-crystal X-ray analysis of the **3k** (Figure 1).[9] The stereochemistries of the minor stereoisomers were determined by analysis of nOe and ^{1}H-^{1}H COSY experiments (for details, see the Supporting Information). This cascade reaction generates six stereogenic centers, and theoretically could give rise to $2^6=64$ different stereoisomers. In fact, we note that this asymmetric cascade reaction forms just three diastereomers, and the least isomers were generally obtained at <10:1 (compared to the major isomers). We rationalize the high stereoselectivity for this cascade reaction as follows: the first Michael addition catalyzed by (*S*)-**4a** is known to proceed with high enantioselectivity; in the second step, the bifunctional base/Brønsted acid catalyst QT-**5a** could activate both the intermediate **A** and the nitroalkene **2**, and promote a highly stereoselective Michael addition again .

In summary, we have developed a highly diastereo- and enantioselective relay cascade Michael/Michael/

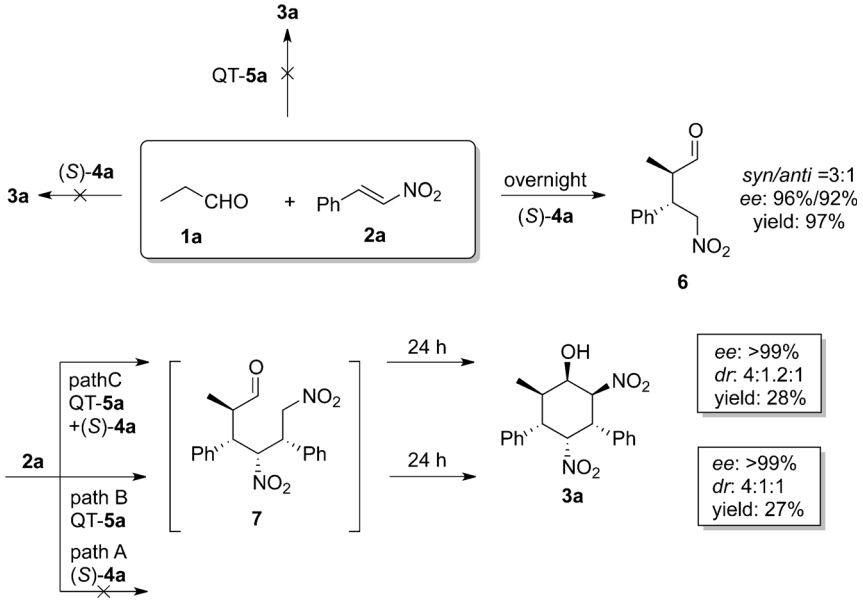
Table 2. Scope of the asymmetric cascade Michael/Michael/Henry reactions.[a]



1a–c 2a–j 3a–o

Entry	**1** (R^1)	**2** (R^2)	Product: Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**1a** (Me)	**2a** (Ph)	**3a**:[f] 60	15:4:1	>99
2	**1b** (Et)	**2a** (Ph)	**3b**: 67	9:2:1	>99
3	**1c** (*n*-Bu)	**2a** (Ph)	**3c**: 57	26:8:1	96
4	**1b** (Et)	**2b** (4-Br-C_6H_4)	**3d**: 70	16:4:1	99
5	**1b** (Et)	**2c** (4-Cl-C_6H_4)	**3e**: 60	18:4:1	>99
6	**1b** (Et)	**2d** (4-CH_3-C_6H_4)	**3f**: 62	11:4: 1	98
7	**1b** (Et)	**2e** (3-MeO-C_6H_4)	**3g**: 55	12:4: 1	>99
8	**1b** (Et)	**2f** (4-MeO-C_6H_4)	**3h**: 47	17:6: 1	>99
9	**1b** (Et)	**2g** (4-F-C_6H_4)	**3i**: 65	14:4:1	>99
10	**1b** (Et)	**2h** (2-naphthyl)	**3j**: 59	29:7:1	98
11	**1a** (Me)	**2b** (4-Br-C_6H_4)	**3k**: 53	16:4: 1	>99
12	**1a** (Me)	**2d** (4-CH_3-C_6H_4)	**3l**: 45	10:3:1	>99
13	**1a** (Me)	**2f** (4-MeO-C_6H_4)	**3m**: 33	49:13: 1	>99
14	**1a** (Me)	**2i** (thiophen-2-yl)	**3n**: 35	15:3:1	99
15[e]	**1a** (Me)	**2j** (5-bromothiophen-2-yl)	**3o**: 34	12:2:1	>99

[a] The reaction was carried out with aldehyde **1** (0.5 mmol), nitroalkene **2** (1.5 mmol), catalyst (*S*)-**4a** (10 mol%), catalyst QT-**5a** (20 mol%) in toluene (1.0 mL) at room temperature for 72 h.
[b] Combined yield of the three stereoisomers.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] The *ee* values for the isolated major products were determined by HPLC on a chiral stationary phase.
[e] The reaction time is 96 h.
[f] The reaction was carried out on an 8-mmol scale with slightly lower yield (54%); 1.15 g of the major stereoisomer **3a** were isolated.



Scheme 2. Probing the mechanism.

Henry reaction catalyzed by combination of readily available diphenylprolinol silyl ether and the quinine thiourea. Under optimal conditions, this reaction could furnish hexasubstituted cyclohexane derivatives from very simple starting materials with excellent control of all six contiguous stereocenters in a one-

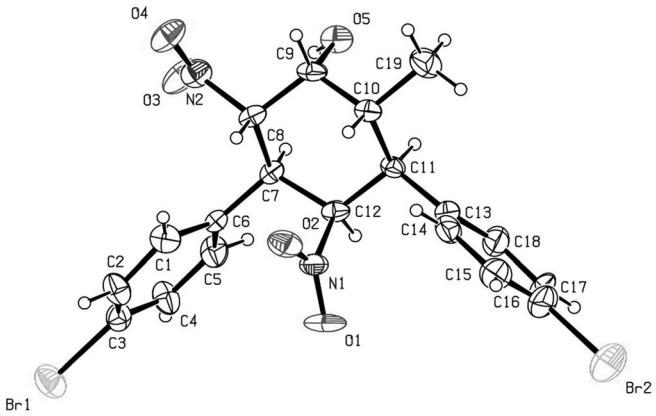


Figure 1. X-ray structure of **3k**.

pot fashion. Hexasubstituted chiral cyclohexanols generated in this asymmetric domino reaction are useful chiral synthetic intermediates since they possess dinitro and the β-hydroxy groups which are important in the asymmetric synthesis of biologically significant compounds.[10]

Experimental Section

Typical Procedure for the Cascade Reaction of Aldehyde 1a and Nitroalkene 2a with Catalyst 4a and Catalyst 5a

To a mixture of catalyst **4a** (0.05 mmol, 10 mol%), catalyst **5a** (0.10 mmol, 20 mol%) in toluene (1.0 mL) was added aldehyde **1a** (0.5 mmol) and nitroalkene **2a** (1.5 mmol). After 72 h of stirring at room temperature, the reaction mixture was directly purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to afford the product **3a** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.99$ (d, $J = 6.6$ Hz, 3H), 2.56 (s, 1H), 3.05–3.16 (m, 1H), 3.52 (dd, $J = 12.3$, 4.5 Hz, 1H), 4.36 (dd, $J = 12.3$, 4.8 Hz, 1H), 4.70 (s, 1H), 5.00 (t, $J = 4.8$ Hz, 1H), 6.10 (dd, $J = 12.3$, 2.4 Hz, 1H), 7.12–7.22 (m, 4H), 7.28–7.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.2$, 33.2, 42.0, 45.4, 72.3, 86.2, 95.1, 127.0, 127.8, 128.2, 128.7, 129.2, 129.4, 134.0, 136.2; IR ($CHCl_3$): $\nu = 3536$, 3328, 2973, 2928, 1550, 1497, 1454, 1374, 1337, 1037, 747, 701 cm^{-1}; HR-MS (ESI): $m/z = 374.1704$, calcd. for $C_{19}H_{20}N_2O_5 + NH_4$: 374.1710; $[\alpha]_D^{28.1}$: +47 (*c* 1.0 in $CHCl_3$); The *ee* value was determined by HPLC on a chiral phase (Chiralpak AD-H column, *n*-hexane/2-propanol 85:15) relative to the racemic sample: major isomer 12.8 min, minor isomer 18.2 min, *ee* > 99%.

Acknowledgements

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[9] CCDC 831031 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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