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Asymmetric Organocatalytic Michael/Michael/Henry Sequence to Construct Cyclohexanes with Six Vicinal Stereogenic Centers

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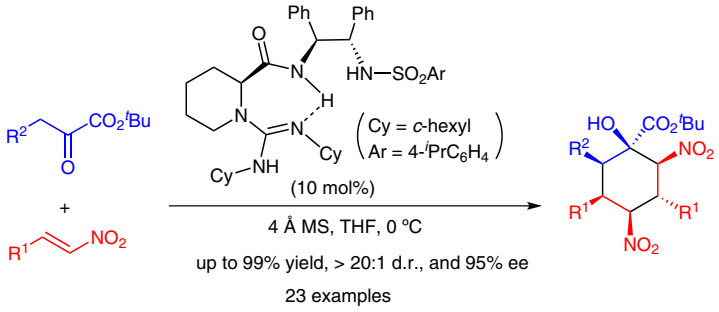

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Abstract An efficient, asymmetric, catalytic, triple-cascade reaction between α-keto esters and nitroalkenes to construct cyclohexanes with six vicinal stereogenic centers in good yields and with high enantioselectivities has been established. A bifunctional guanidine–amide organocatalyst proved to be useful for the Michael/Michael/Henry sequence through Brønsted base and hydrogen-bonding cooperative catalysis.

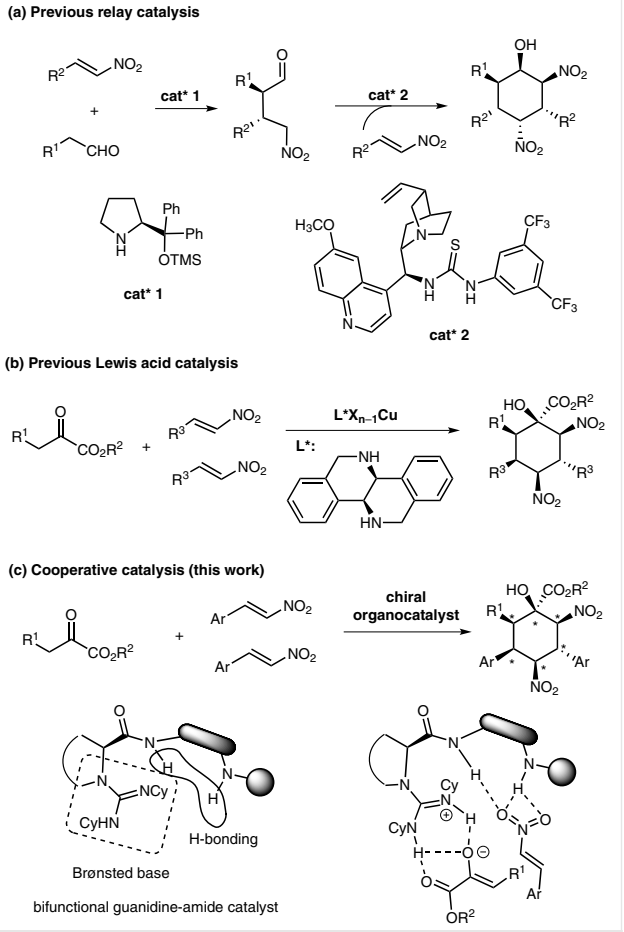
Key words asymmetric catalysis, cascade reaction, cyclohexanes, organocatalysis, keto esters, nitroalkenes

The field of asymmetric organocatalysis is a rapidly expanding and important field in organic chemistry.[1] In part, organocatalytic cascade or domino reactions constitute an efficient and powerful synthetic tool for the construction of molecular complexity.[2] For example, the iminium–enamine combination in the field of amine-catalyzed cascade reactions permits double, triple, or even quadruple processes for the synthesis of complex and valuable synthetic building blocks.[3] Other activation modes, such as hydrogen bonding, protonation, and umpolung, have also been established, but are generally limited to the promotion of simple cascade reactions.[4] Bifunctional or multifunctional organocatalysts possess multiple activation modes, which can be envisaged to participate in a broad variety of possible cascade reactions.[5]

Recently, organocatalytic cascade approaches to enantiomerically enriched multisubstituted cyclohexane derivatives have attracted a great deal of attention, owing to the prevalence of such motifs in pharmaceutical compounds and complex natural products.[6] Organocatalytic asymmetric domino reactions for concise syntheses of tetra- or pentasubstituted cyclohexane derivatives have been achieved.[6c,d,f,g–j,l,m] Although a Michael/Michael/Henry sequence between aldehydes and nitroalkenes has been used to synthesize hexasubstituted cyclohexanes, two kinds of organocatalyst are needed to complete the cyclization (Scheme 1, a).[6l] A similar process between an α-keto ester and a nitroalkene might generate a cyclohexane with six stereocenters, including a quaternary center, in one pot.[7] Such asymmetric catalysis was first realized by the use of a chiral Lewis acid catalyst, assisted by an organic base as the cocatalyst in some cases (Scheme 1, b).[7a] However, no single chiral organocatalyst has been employed in this cascade reaction.

In the past few years, our group has developed a series of bifunctional chiral guanidine catalysts that are effective in Michael reactions, Mannich-type reactions, Henry reactions, and others.[8] In most cases, vicinal stereocenters can be constructed with high diastereo- and enantioselectivities. These primary contributions suggested that a combination of Brønsted base catalysis and hydrogen-bonding catalysis with a guanidine-based catalyst would be of particular interest in triple-cascade extensions. We found that the guanidine unit of the chiral guanidine–amide catalysts promotes the deprotonation of α-keto ester and nitroalkane intermediates, generating the corresponding carbon nucleophiles. Meanwhile, the amide unit activates the electrophile by forming a hydrogen bond, thereby inducing a triple process actively and stereoselectively (Scheme 1,c). Here, we describe a new chiral organocatalyst for the asymmetric sequential Michael/Michael/Henry reaction that permits the consecutive formation of hexasubstituted cyclohexane derivatives with one quaternary stereocenter in good yield, excellent diastereoselectivity, and high enantioselectivity.

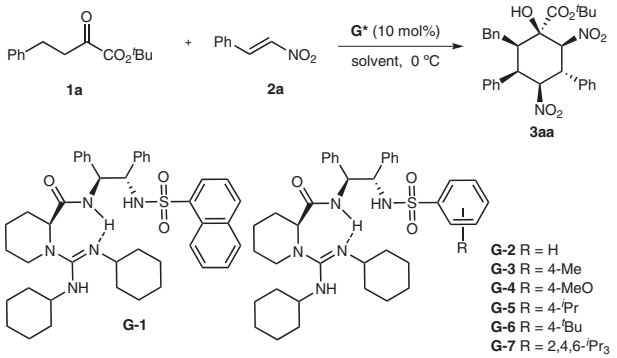
Starting from α-keto ester **1a** and nitroalkene **2a**, and employing the bifunctional guanidine catalyst **G-1** in toluene as the solvent, we obtained the desired cyclohexane de-



Scheme 1 Asymmetric catalytic Michael/Michael/Henry sequence for the synthesis of hexasubstituted cyclohexanes

rivative **3aa** in 37% yield, >20:1 dr, and 77% ee (Table 1, entry 1). Further investigations focused on the solvent, and we found that THF gave good results in terms of reactivity and enantioselectivity (entries 1–3). Subsequently, we examined the substituent on the sulfonamide unit of the chiral guanidine catalyst (entries 3–9). The results showed that the sulfonamide substituent had obvious effects on both the reactivity and enantioselectivity. The introduction of a substituent at the *para*-position of the benzenesulfonamide benefited the enantioselectivity, but the reactivity decreased as the steric hindrance of the substituent increased (entries 4–8). When guanidine **G-6** bearing a 4-*tert*-butylbenzenesulfonamide unit was used, only 10% yield of the desired product **3aa** was obtained, without loss of enantioselectivity (entry 8). Embedding a sterically hindered 2,4,6-triisopropylbenzenesulfonamide into catalyst **G-7** gave a sharp drop in enantioselectivity (entry 9). The use of guanidine **G-5** in the presence of 4 Å molecular sieves gave the cascade product in an improved yield of 71% without a decrease in the enantiomeric excess (entry 10); this was subsequently optimized to 80% yield and 90% ee by reducing the amount of the solvent (entry 11). Note that the order of addition of the two reactants had an obvious influence on the result (entry 12): when α-keto ester **1a** and catalyst **G-5** were mixed beforehand, with subsequent addition of nitroalkene **2a** at 0 °C, a yield of 93% with 90% ee was obtained.

Table 1 Optimization of the Reaction Conditions[a]



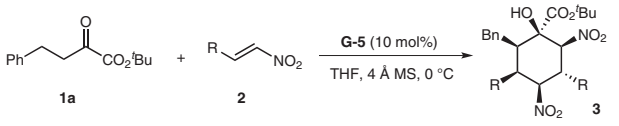
Entry	Catalyst	Solvent	Yield[b] (%)	dr[c]	ee[d] (%)
1	**G-1**	toluene	37	>20:1	77
2	**G-1**	Et_2O	34	>20:1	83
3	**G-1**	THF	49	>20:1	84
4	**G-2**	THF	55	>20:1	81
5	**G-3**	THF	72	>20:1	87
6	**G-4**	THF	60	>20:1	87
7	**G-5**	THF	54	>20:1	90
8	**G-6**	THF	10	>20:1	90
9	**G-7**	THF	69	>20:1	65
10[e]	**G-5**	THF	71	>20:1	90
11[f]	**G-5**	THF	80	>20:1	90
12[g]	**G-5**	THF	93	>20:1	90

[a] Reaction conditions: **G** (10 mol%), **1a** (0.1 mmol), **2a** (3.0 equiv), solvent (1.0 mL), 0 °C, 3 d.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.
[e] 4 Å MS (20 mg) were added.
[f] 4 Å MS (20 mg) and THF (0.5 mL) were used.
[g] **G-5** (10 mol%), 4 Å MS (20 mg), and **1a** (0.10 mmol) were stirred in THF (0.5 mL) at 0 °C for 30 min, then **2a** (3.0 equiv) was added.

With the optimal conditions, we next studied the scope of the reaction (Table 2). In general, the reactions occurred with various β-aryl-substituted nitroalkenes bearing electron-withdrawing or -donating substituents at various positions, yielding the corresponding products **3** in good yields (56–99%) and with excellent stereoselectivities (84–95% ee, >20:1 dr; entries 1–11). The electronic nature of the substituent on the benzyl group had an obvious effect on the outcome, with electron-donating substituents giving higher yields than electron-withdrawing substituents (en-

tries 8–11). Notably, slightly better enantioselectivities were obtained when *ortho*-substituted β-nitrostyrenes were subjected to the formal [2+2+2] tandem annulation process (entries 2, 8, and 9). These results are a useful complement to a previously reported reaction in which a chiral Lewis acid catalyst gave a 76% yield and 60% ee of product **3ai**.[7a] Both 3-furyl- and 2-furyl-substituted substrates were tolerated in the reaction, and the corresponding cycloaddition products **3al** and **3am** were obtained in 94% and 93% yield, respectively, and with 85% and 83% ee, respectively (entries 12 and 13). Furthermore, a 1-naphthyl-substituted nitroalkene afforded the corresponding product **3an** in a higher yield and better enantioselectivity than did a 2-naphthyl-substituted nitroalkene (entries 14 and 15).

Table 2 Substrate Scope of the Nitroalkenes[a]

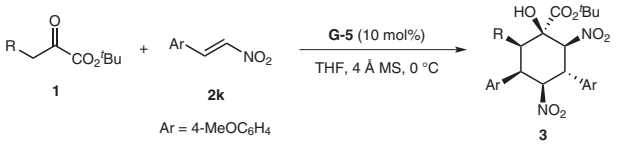


Entry	R	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	**3aa**	93	>20:1	90
2	2-FC_6H_4	**3ab**	95	>20:1	92
3	4-FC_6H_4	**3ac**	88	>20:1	88
4	4-ClC_6H_4	**3ad**	73	>20:1	90
5	4-BrC_6H_4	**3ae**	77	>20:1	91[e]
6	4-$F_3CC_6H_4$	**3af**	84	>20:1	88
7	3,4-$Cl_2C_6H_3$	**3ag**	56	>20:1	84
8	2-Tol	**3ah**	91	>20:1	95
9	2-$MeOC_6H_4$	**3ai**	99	>20:1	91
10	3-$MeOC_6H_4$	**3aj**	88	>20:1	90
11	4-$MeOC_6H_4$	**3ak**	96	>20:1	92
12	3-furyl	**3al**	94	>20:1	85
13	2-furyl	**3am**	93	>20:1	83
14	1-naphthyl	**3an**	99	>20:1	90
15	2-naphthyl	**3ao**	86	>20:1	87

[a] All reactions were performed with **1a** (0.1 mmol) and **2** (0.3 mmol) under the standard conditions (Table [1], entry 12).
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.
[e] The absolute configuration of **3ae** was determined to be (1*R*,2*R*,3*R*,4*S*,5*R*,6*S*) by comparison with the authentic compound.[7a]

Next, we applied the catalytic system to various α-keto esters to define the scope of the one-pot procedure. As shown in Table 3, the reaction between α-keto ester **1b** bearing a 4-fluorophenyl substituent and nitroalkene **2k** proceeded well to give product **3bk** in 99% yield and 90% ee (entry 1). When 3-phenylpropyl or 4-phenylbutyl α-keto esters were employed in the reaction, 99% and 83% yields with 89% and 88% ee were obtained, respectively (entries 2 and 3). Meanwhile, a chained alkene group or linear or branched alkyl chains in the α-keto ester had no obvious effect on the enantioselectivity, and the corresponding hexasubstituted cyclohexane isomers were obtained in satisfactory yields and enantioselectivities (74–92% yield, 88–90% ee; entries 4–8).

Table 3 Substrate Scope of the α-Keto Esters[a]



Entry	R	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	4-$FC_6H_4CH_2$	**3bk**	99	>20:1	90
2	$Ph(CH_2)_2$	**3ck**	99	>20:1	89
3	$Ph(CH_2)_3$	**3dk**	83	>20:1	88
4	CH_2=$CHCH_2$	**3ek**	79	>20:1	90
5	CH_2=$CH(CH_2)_2$	**3fk**	88	>20:1	88
6	Bu	**3gk**	87	>20:1	90
7	*i*-Bu	**3hk**	92	>20:1	90
8	$Me(CH_2)_4$	**3ik**	74	>20:1	88

[a] All reactions were performed with **1** (0.1 mmol) and **2k** (0.3 mmol) under the standard conditions.
[b] Isolated yields.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.

In summary, we have developed an organocatalyzed Michael/Michael/Henry cascade strategy for the simple construction of cyclohexane structures containing six vicinal stereocenters.[9,10] The reaction proceeds with high to excellent diastereo- and enantioselectivities (more than 20:1 dr and up to 95% ee). The accessibility of the starting α-keto esters and the easy manipulation of the organocatalytic system make this system attractive. Further work aims to expand this concept to the asymmetric synthesis of more-complex useful molecular structures.

Acknowledgment

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(9) **Hexasubstituted Cyclohexanes 3aa–3ik; General Procedure**
Guanidine **G-5** (10 mol%), α-keto ester **1** (0.1 mmol), and 4 Å MS (20 mg) were weighed into a test tube under N_2. THF (0.5 mL) was added and the solution was stirred for 0.5 h at 0 °C. Nitroalkene **2** (0.3 mmol) was then added at 0 °C, and the resulting mixture was stirred for 3 d at 0 °C to give the product **3**, which was purified by flash chromatography.

(10) ***tert*-Butyl (1*R*,2*R*,3*R*,4*S*,5*R*,6*S*)-2-Benzyl-1-hydroxy-4,6-dinitro-3,5-diphenylcyclohexanecarboxylate (3aa)**
White solid; yield: 51.7 mg (93%, 90% ee, >20:1 dr); mp 162 °C; $[\alpha]_D^{29}$ +45.3 (*c* 0.47, CH_2Cl_2); HPLC: [Daicel CHIRALCEL IA; hexane–*i*-PrOH (85:15); flow rate = 1.0 mL/min; λ = 210 nm]: t_R = 7.33 min (minor), 12.59 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.08 (m, 13 H), 6.78 (d, *J* = 7.2 Hz, 2 H), 5.22–5.16 (m, 1 H), 5.10 (dd, *J* = 12.4, 6.4 Hz, 1 H), 4.49 (t, *J* = 12.4 Hz, 1 H), 4.18 (s, 1 H), 3.54 (t, *J* = 6.4 Hz, 1 H), 2.95 (s, 1 H), 2.54–2.36 (m, 2 H), 1.59 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 137.4, 134.9, 132.1, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3 127.0, 92.7, 90.3, 86.6, 77.7, 47.1, 45.7, 40.3, 33.7, 27.9. HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{30}H_{32}N_2NaO_7^+$: 555.2102; found: 555.2101.

***tert*-Butyl (1*R*,2*R*,3*R*,4*S*,5*R*,6*S*)-2-Benzyl-1-hydroxy-4,6-dinitro-3,5-bis(2-tolyl)cyclohexanecarboxylate (3ah)**
White solid; yield: 53.0 mg (91%, 95% ee, >20:1 dr); mp 140 °C; $[\alpha]_D^{26}$ +72.6 (*c* 1.26, CH_2Cl_2); HPLC: [Daicel CHIRALCEL IA; hexane–*i*-PrOH (85:15); flow rate = 1.0 mL/min; λ = 210 nm]: t_R = 10.21 min (minor), 16.58 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 7.6 Hz, 1 H), 7.24–7.08 (m, 8 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 6.74 (d, *J* = 6.0 Hz, 2 H), 5.27 (t, *J* = 12.0 Hz, 2 H), 4.88 (t, *J* = 12.0 Hz, 1 H), 4.35 (s, 1 H), 4.16 (t, *J* = 6.4 Hz, 1 H), 3.26 (s, 1 H), 2.65–2.53 (m, 1 H), 2.50 (s, 3 H), 2.49–2.32 (m, 1 H), 1.64 (s, 9 H), 1.32 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 140.0, 139.3, 137.0, 133.2, 131.7, 131.3, 131.2, 131.1, 129.0, 128.8, 128.1, 128.0, 126.9, 126.3, 126.2, 124.0, 93.1, 90.8, 86.5, 77.8, 45.2, 39.8, 34.8, 33.5, 27.9, 19.5, 19.3. HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{32}H_{36}N_2NaO_7^+$: 583.2415; found: 583.2415.