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A Highly Diastereoselective Tertiary Amine-Catalyzed Cascade Michael–Michael–Henry Reaction between Nitromethane, Activated Alkenes and α,β-Unsaturated Carbonyl Compounds

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Abstract: A new tertiary amine-catalyzed cascade Michael–Michael–Henry reaction between nitromethane, a doubly activated alkene and an α,β-unsaturated carbonyl compound is described, which provides a convenient and efficient synthesis for densely functionalized cyclohexanes and some bicyclic compounds in moderate to excellent yields with high diastereoselectivity.

Keywords: activated alkenes; cascade reactions; multicomponent reactions; nitromethane; organocatalysis

Organocatalysis has grown rapidly to become one of the most exciting and current fields in contemporary organic chemistry.[1] Besides such characteristics as being metal-free, usually non-toxic, readily available, and often robust, a significant advantage of many organocatalysts like secondary amines is the capability of promoting several types of reactions through different activation modes.[1c,2] This ability makes an organic catalyst ideal for application in cascade/domino reactions, which provide an efficient means to construct complex molecules from simple precursors in a single process. As well-recognized, domino reactions avoid time-consuming and costly protection/deprotection processes and the purification of intermediates as well.[3] Intrinsically, organocatalytic domino reactions inherit such advantages from both the organocatalysis and the domino reaction, featuring high synthetic efficiencies and green chemistry factors.[1c,4] It is not astonishing that organocatalytic domino reactions represent a new and active area in organic chemistry. Many interesting reactions with high chemo- and stereoselectivity have been developed during the past few years.[5]

Among the reported organocatalytic domino reactions,[1c,4] most of them involve a two-step cascade, in which the first step is intermolecular and the second is intramolecular. The recently reported double cascade modes include Michael–Michael reaction,[5a–e] Michael-aldol reaction,[5f,g] Michael–Henry reaction,[5h–m] Michael–Morita–Baylis–Hillman reaction,[5n] Michael-alkylation reaction,[5o,p] Knoevenagel–Diels–Alder reaction,[5q] and others.[5r–t] Such organocatalytic domino reactions with a triple or higher cascade sequence, however, have been much less explored,[6] although a pioneering magnum opus involving a triple cascade course was disclosed by Enders et al. in 2006.[6a] Theoretically, by manipulating the functionality on the substrates with an adequate arrangement, much higher-order cascade and multi-component reactions can be achieved. Therefore, the development of innovative higher-order cascade sequences to achieve better synthetic efficiencies is highly desirable.

Both the Michael addition reaction[7] and the Henry reaction[8] are most important carbon-carbon bond forming tools with the capability to readily implement useful functionality into the target molecule. Combining these two reactions into a synthetic cascade should be a highly efficient strategy to construct densely functionalized building blocks. In the past few years, several pioneering organocatalytic domino reactions involving both Michael addition and Henry reaction in a sequence were reported, demonstrating the high efficiency of this strategy in organic synthesis.[5h–m,6i,m]

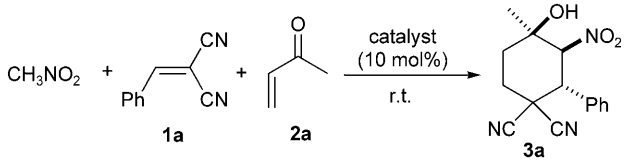
In conjunction of our efforts on exploring new carbon-carbon bond forming reactions *via* nucleophilic organocatalysis,[9] we intended to investigate the Lewis base-catalyzed cross-coupling between different

activated alkenes, since this type of coupling is still challenging for the organic chemistry community due to the inherent preference of the homo-coupling over the desired hetero-coupling. Encouragingly, some successful examples of organocatalytic cross-coupling between two different activated olefins have been recently developed by Shi[10] and other groups.[5e,6e] Herein, we wish to report a new tertiary amine-catalyzed cascade Michael–Michael–Henry reaction between nitromethane, doubly activated alkenes and α,β-unsaturated carbonyl compounds, which provides a convenient and efficient synthetic approach for polyfunctionalized cyclohexanes and some bicyclic compounds.

Our investigation was initiated with the model reaction between phenylmethylidenemalononitrile (**1a**), methyl vinyl ketone (**2a**) and nitromethane. Gratifyingly, a three-component annulation reaction between these substrates occurred, affording the densely functionalized cyclohexane **3a** (Table 1). Preliminary optimization of the reaction conditions revealed that a few nucleophilic organic Lewis bases such as PPh_3, DMAP (4-*N*,*N*-dimethylaminopyridine), imidazole, DABCO (1,4-diazabicyclo[2.2.2]octane), and triethylamine were effective and better yields were obtained in toluene with DABCO and triethylamine (Table 1, entries 1, 3–6). Conversely, the non-nucleophilic Lewis base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)[11] and the weak inorganic base potassium carbonate were both ineffective for this reaction (entries 2 and 7). However, use of a strong base like potassium *tert*-butoxide also resulted in the formation of **3a** in a low yield (entry 8). Further screening of solvents was carried out with common solvents (entries 9–16), and a protic solvent, 2-propanol, emerged as the best, giving **3a** in 84% yield (entry 10).

With optimized conditions in hand, the substrate scope was then tested. Acyclic α,β-unsaturated carbonyl compounds like methyl vinyl ketone (**2a**) and acrolein (**2b**) were both effective in the reaction (Table 2). Under the catalysis of Et_3N (10 mol%) and at room temperature, both aryl- and heteroaryl-substituted methylenemalononitriles (**1a–k**) smoothly underwent a three-component annulation reaction with nitromethane and **2a**, giving polysubstituted cyclohexanes **3a–k** as a single diastereomer in 61–95% yields after a single column chromatographic isolation (Table 2, entries 1–11). Under similar conditions, the aliphatic cyclohexyl-substituted methylenemalononitrile (**1l**) also gave rise to the corresponding cyclohexane **3l** in 69% yield, although an elongated reaction time (24 h) was required (entry 12). For acrolein **2b**,

Table 1. Screening of the catalyst and solvent.[a]



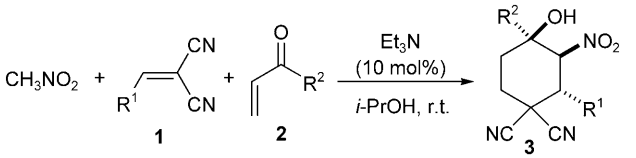
Entry	Catalyst	Solvent	Yield of **3a** [%][b]
1	PPh_3	toluene	25
2	DBU	toluene	trace
3	DMAP	toluene	21
4	imidazole	toluene	44
5	Et_3N	toluene	66
6	DABCO	toluene	63
7	K_2CO_3[c]	toluene	trace
8	*t*-BuOK	toluene	21
9	DABCO	*i*-PrOH	50
10	Et_3N	*i*-PrOH	84
11	Et_3N	$CHCl_3$	32
12	Et_3N	THF	49
13	Et_3N	DMF	18
14	Et_3N	CH_3CN	36
15	Et_3N	1,4-dioxane	31
16	Et_3N	ether	11

[a] *Reaction conditions:* unless otherwise noted, a mixture of nitromethane (2.5 mmol), phenylmethylene malononitrile **1a** (0.5 mmol), methyl vinyl ketone **2a** (0.6 mmol), and the catalyst (0.05 mmol) in the specified solvent (2.0 mL) was stirred at room temperature for 24 h (entries 1–8) or 6 h (entries 9–16).

[b] Isolated yield as a single diastereomer based on **1a**.

[c] The catalyst loading was 1.0 mmol.

Table 2. Synthesis of densely functionalized cyclohexanes **3** from acyclic α,β-unsaturated carbonyl compounds.[a]



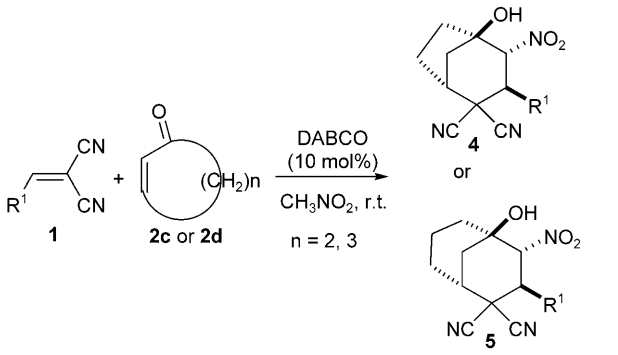
Entry	R^1	R^2	Time [h]	Yield [%][b]
1	C_6H_5 (**1a**)	CH_3	6	**3a**, 84
2	*p*-$CH_3C_6H_4$ (**1b**)	CH_3	7	**3b**, 88
3	*p*-$CH_3OC_6H_4$ (**1c**)	CH_3	4.5	**3c**, 95
4	*p*-ClC_6H_4 (**1d**)	CH_3	9	**3d**, 71
5	*o*-ClC_6H_4 (**1e**)	CH_3	6	**3e**, 77
6	*p*-FC_6H_4 (**1f**)	CH_3	4	**3f**, 82
7	*p*-$CF_3C_6H_4$ (**1g**)	CH_3	4.5	**3g**, 61
8	*p*-$NO_2C_6H_4$ (**1h**)	CH_3	4	**3h**, 91
9	3-pyridyl (**1i**)	CH_3	12	**3i**, 69
10	2-furyl (**1j**)	CH_3	20	**3j**, 82
11	2-thienyl (**1k**)	CH_3	3	**3k**, 87
12	cyclohexyl (**1l**)	CH_3	24	**3l**, 69
13[c]	C_6H_5 (**1a**)	H	36	**3m**, 52
14[c]	*p*-ClC_6H_4 (**1d**)	H	24	**3n**, 44

[a] For experimental details, see Experimental Section.

[b] Isolated yield based on **1**.

[c] The catalyst DABCO (0.05 mmol) was used instead.

Table 3. Synthesis of densely functionalized bicyclic compounds **4** and **5** from cyclic α,β-unsaturated ketones.[a]



Entry	R^1	n	Time [h]	Yield [%][b]
1	C_6H_5	2 (**2c**)	12	**4a**, 57
2	*p*-$CH_3C_6H_4$	2 (**2c**)	6	**4b**, 62
3	*p*-$CH_3OC_6H_4$	2 (**2c**)	52	**4c**, 66[c]
4	*p*-$NO_2C_6H_4$	2 (**2c**)	14	**4d**, 65[c]
5	2-furyl	2 (**2c**)	48	**4e**, 74[c]
6	C_6H_5	3 (**2d**)	12	**5a**, 45
7	2-furyl	3 (**2d**)	12	**5b**, 48

[a] For experimental details, see Experimental Section.
[b] Isolated yield based on **1**.
[c] The reaction was run with nitromethane (1.5 mmol) in 2-propanol (2.0 mL).

the catalyst DABCO (10 mol%) was best used to effect the annulation with selected arylmethylidene malononitriles (**1a**, **1d**), affording the corresponding cyclohexanes **3m** and **3n** in moderate yields (entries 13 and 14).

In Table 3 are summarized the results from the investigation on cyclic α,β-unsaturated ketones. Conjugated cyclopentenone (**2c**) and cyclohexenone (**2d**) were both effective substrates: under mild conditions and the catalysis of DABCO (10 mol%), both cyclic ketones **2c** and **2d** readily underwent a three-component annulation with the representative aryl- or heteroaryl-substituted methylenemalononitriles **1** and nitromethane, giving the corresponding highly functionalized bicyclo[3.2.1]octanes **4** and bicyclo[3.3.1]nonanes **5** as a single diastereomer in modest yields. In comparison with those carried out with a 3-fold amount of nitromethane in 2-propanol (entries 3–5), the reaction rates were remarkably accelerated when the annulation was run in excess nitromethane as solvent (Table 3, entries 1, 2, 6 and 7), but the yields of the bicyclic products were not obviously enhanced. The bicyclic compounds **4** and **5** with a hydroxy group positioned at a bridgehead carbon represent important structural components in some biologically interesting alkaloids,[12] and few tandem or domino sequences have been before reported for construction of these characteristic bicyclic frameworks.[13] This organocatalytic three-component annulation of cyclic unsaturated ketones provides a novel and convenient synthetic method for the type of bicyclic system. Also, the diverse functionality including versatile nitro and cyano groups in products **4** and **5** will facilitate further organic transformations on them.

Under the optimized conditions, other nitroalkanes than nitromethane were also surveyed. Under the catalysis of either triethylamine or DABCO (10–20 mol%), neither nitroethane nor 2-phenyl-1,3-dinitropropane gave any expected annulation products with activated olefin **1a** and α,β-unsaturated ketone **2a** or **2c**. The dependence of this amine-catalyzed annulation on the substrates including nitroalkane, doubly activated olefin and α,β-unsaturated carbonyl compound deserves more efforts to further explore.

The structures of cyclohexanes **3** and bicyclics **4** and **5** were identified by ^1H and ^{13}C NMR spectroscopy, as well as X-ray crystallography in some cases (for **3d** and **3n**: CCDC 742978 and 742979 contain 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. For spectroscopic data of all new compounds, see Supporting Information). For all of the compounds **3**, **4** and **5**, a large axial coupling constant ($^3J_{H,H}$ = *ca.* 12.0 Hz) between two adjacent hydrogens which are located respectively at the R^1 and nitro-substituted carbons was observed. This observation confirmed the assignment of a *trans*-configuration with respect to R^1 and the nitro groups. For cyclohexanes **3**, a *cis*-configuration for hydroxy and nitro groups was assigned by a small equatorial coupling constant ($^3J_{H,H}$ = *ca.* 2.4 Hz) between two vicinal hydrogens in the cyclohexane ring (**3m**, **3n**), and by X-ray crystallographic analysis (**3d**, **3n**) as well. For bicyclic compounds **4** and **5**, however, the hydroxy group occupies a *trans* position against the nitro group, as identified by their ^1H NMR data including NOESY analysis (see Supporting Information).

In all cases, the annulation products (**3**, **4**, or **5**) were obtained in moderate to excellent yields as a single diastereomer after conventional column chromatographic isolation. Other diastereomers were not detected even in crude products from those clean annulation reactions (such as **3a–c**, **3h**) by ^1H NMR spectroscopy. This stereochemical outcome, as well as

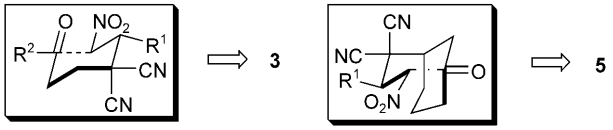
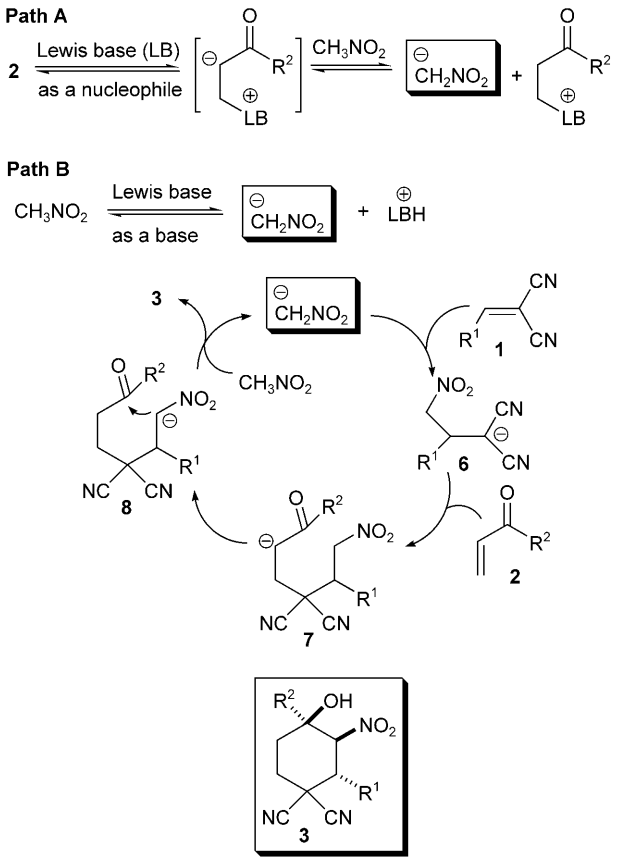


Figure 1. Proposed chair conformations leading to the stereochemical outcomes in representative products **3** and **5**.

the high diastereoselectivity, could be rationalized in terms of the conformational stability of the six-membered ring transition state (Figure 1). The importance of the conformational stability in the highly stereoselective construction of polysubstituted cyclohexanes has been demonstrated in a few cascade reactions.[5h,i,6a,c,14]

Although the exact mechanism for this three-component annulation reaction remains unclear, on the basis of the experimental results in this study, a proposed mechanism is shown in Scheme 1. Presumably, the annulation reaction is initiated with the generation of a nitrocarbanion. Even though the possibility could not be completely ruled out that the catalyst Lewis base (LB) acts as a base in the deprotonation of nitromethane (Path B), it is most likely that the catalyst LB acts as a nucleophilic trigger which undergoes a Michael addition to the unsaturated carbonyl compound **2**, leading to the formation of a strongly basic zwitterionic enolate intermediate. Subsequently, the enolate base deprives nitromethane of a proton to produce the nitrocarbanion (Path A). Similar mechanisms for the generation of a strong base by use of a strong nucleophile have been documented before.[11b,15] Additionally, results from the catalyst screening (Table 1) are consistent with this proposal: those nucleophilic Lewis bases including basic amines and weakly basic phosphanes are effective for the annulation model reaction; in contrast, the non-nucleophilic DBU and weak inorganic base K_2CO_3 are ineffective.

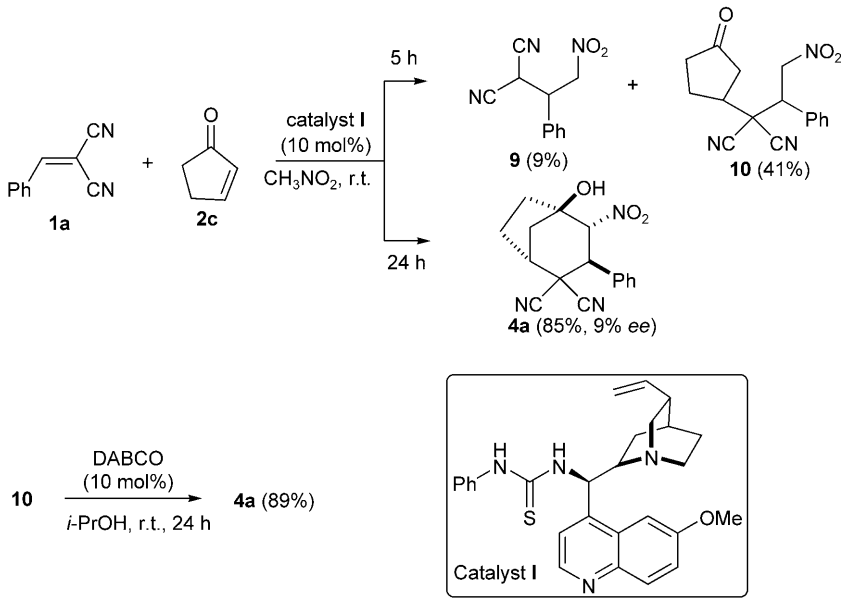


Scheme 1. A plausible catalytic cycle of the three-component cascade annulation.

A catalytic cycle for the three-component annulation is then proposed as follows: the nitrocarbanion first reacts with substituted methylenemalononitrile **1** to afford a Michael adduct **6**, which subsequently undergoes another Michael addition to the unsaturated carbonyl compound **2**, leading to the formation of a double Michael addition product **7**. Intermediate **7** then converts to intermediate **8** *via* a proton transfer. An intramolecular Henry reaction of intermediate **8**, followed by protonation with nitromethane, accomplishes the formation of the annulation product **3** and the regeneration of the nitrocarbanion (Scheme 1).

The following experimental results provide solid evidence for the above catalytic cycle (Scheme 2). Under the same reaction conditions for the preparation of **4a** – except that the catalyst **I** was used instead – the reaction between **1a**, **2c** and nitromethane was re-investigated. After 5 h, the reaction was quenched and consequently the first Michael adduct **9** and the double-Michael adduct **10** were isolated in 9% and 41% yields, respectively. In another scenario, when the reaction was run continuously for 24 h, the final annulation product **4a** was obtained in 85% yield with slight enantioselectivity (9% *ee*). In comparison, under the catalysis of DABCO (10 mol%), the isolated **10** was readily converted into **4a** in 89% yield. These results definitely imply that this three-component annulation reaction proceeds in a triple Michael–Michael–Henry cascade sequence which comprises two intermolecular steps and one intramolecular step.

In conclusion, a highly diastereoselective tertiary amine-catalyzed three-component annulation reaction between nitromethane, doubly activated alkenes and α,β-unsaturated carbonyl compounds has been demonstrated, which provides convenient and efficient accesses toward densely functionalized cyclohexanes and bicyclic frameworks including those of the bicyclo[3.2.1]octane and bicyclo[3.3.1]nonane type. On the basis of the experimental results in this study, this organocatalytic annulation reaction supposedly proceeds in a Michael–Michael–Henry cascade course. It represents an efficient and higher-order cascade mode: a three-component and triple cascade comprising two intermolecular steps and one intramolecular step. Further studies on this reaction in our laboratory will be directed towards its asymmetric variant, generality and application in organic synthesis. Results from such investigations will be reported in due course.



Scheme 2. Isolation and Identification of intermediates **9** and **10**.

Experimental Section

Synthesis of Cyclohexanes 3 (General Procedure)

To a stirred mixture of α,β-unsaturated carbonyl compound **2a** or **2b** (0.6 mmol), nitromethane (2.5 mmol) and the amine catalyst Et_3N (0.05 mmol, for **3a–l**) or DABCO (0.05 mmol, for **3m**, **n**) in *i*-PrOH (2.0 mL), was added the substituted methylenemalononitrile **1** (0.05 mmol) at room temperature. The resulting reaction mixture was vigorously stirred until **1** was completely consumed (monitored by TLC). The solvent and volatile components were then removed on a rotary evaporator under reduced pressure and the residue was subjected to column chromatography on silica gel (eluant: petroleum ether/ethyl acetate 5:1, v/v) to give diastereomerically pure **3** (Table 2).

Synthesis of Bicyclo[3.2.1]octanes 4 and Bicyclo[3.3.1]nonanes 5 (General Procedure)

A mixture consisting of cyclopentenone **2c** or cyclohexenone **2d** (1.0 mmol), substituted methylenemalononitrile **1** (0.5 mmol), and the catalyst DABCO (0.05 mmol) in nitromethane (2.0 mL) was vigorously stirred at ambient temperature until **1** had disappeared, as monitored by TLC. The volatile components in the reaction mixture were removed on a rotary evaporator under reduced pressure and the crude product was purified by column chromatography on silica gel (gradient eluant: petroleum ether/ethyl acetate, 8:1–5:1) to afford diastereomerically pure **4** or **5** (Table 3).

Detailed experimental procedures, full spectroscopic data (^1H, ^{13}C NMR, FT-IR and HR-MS) for new compounds including **3**, **4** and **5**, and X-ray diffraction data are presented in the Supporting Information.

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