One-pot cascade Michael–Michael–Aldol condensation for diastereoselective synthesis of nitro-substituted cyclohexanes†

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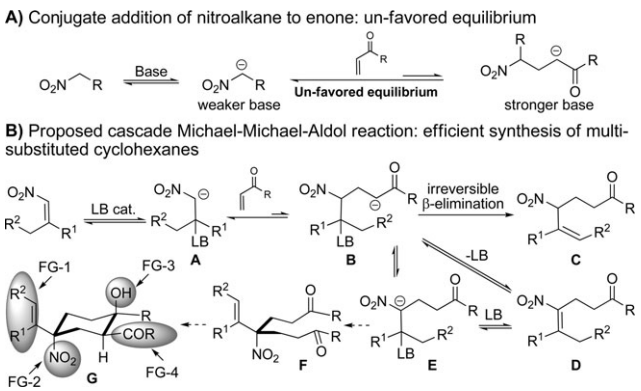
A one-pot reaction of nitroalkenes and enones was developed for the preparation of nitro-vinyl-substituted cyclohexanes, which could be simply converted into poly-*N*-heterocycles.

Cascade processes have a long tradition as efficient approaches in complex molecule synthesis.[1] Compared to the Lewis acid-, radical- and transition metal-promoted cascade reactions, Lewis base (LB)-mediated cascade transformations are much less studied. However, with their unique reaction mechanisms, successful LB-mediated cascade processes can provide new approaches for complicated molecule construction that are difficult to achieve using other methods.[2]

Our interest in developing LB-mediated cascade reactions was initiated by the investigation of nitroalkene conjugate addition. With the presence of a more acidic proton, addition of the nitro compound to the enone was unfavored (formation of stronger base) if no other reagents were added (Scheme 1A). However, this transformation is attractive, since it provides different 1,4-difunctional building blocks that can be further converted into synthetically useful complex molecules.[3] Herein, we report a successful Michael–Michael–aldol cascade reaction of nitroalkenes and enones for the synthesis of functional group-enriched cyclohexanes with excellent yields, and its application in the preparation of poly-*N*-heterocycles (Scheme 1B).



Scheme 1 Lewis base activation of nitroalkenes.

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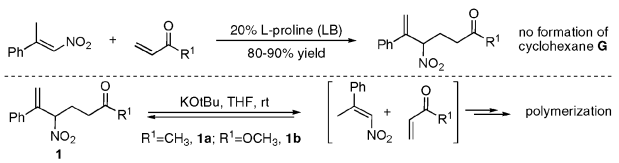
† Electronic supplementary information (ESI) available: Experimental details, X-ray measurement, and ^{1}H NMR and ^{13}C NMR for all compounds. CCDC 728930–728934. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/b909766j

Nitroalkenes are important synthetic building blocks due to their versatile reactivity in producing diverse functional groups through easy transformations.[4] According to literature, nitroalkenes are commonly used as electrophiles or electron-deficient dienophiles.[5] The Lewis base activation of nitroalkenes provides a new and interesting strategy, whereby the resulting nitro carbanion, **A**, serves as a nucleophile for subsequent reaction with an appropriate electrophile. However, one big challenge with this design is the homo-condensation of nitroalkenes, leading to their polymerization.[6] To solve this problem, our group recently developed an alternative β-elimination approach, producing the allylic nitro compound, **C**, as shown in Scheme 1B.[7] The key to the success of this new strategy is *the introduction of one irreversible step in the overall equilibrium system*. Various β-alkyl nitroalkenes were suitable for this reaction, which made this transformation an efficient new approach in C–C bond formation for the preparation of 1,4-difunctional products.

Encouraged by this result, we wondered whether this new cascade process could be further extended to a second Michael addition and subsequent intramolecular aldol reaction, leading to nitro-substituted cyclohexane **G** in one-pot, as shown in Scheme 1B. This proposed cascade condensation is very attractive since the resulting nitro-substituted cyclohexanes can be readily converted into functional group enriched *N*-heterocycles through simple steps. Moreover, the mechanism revealed through this process will help the understanding of the key factors that control this rather complex multi-component systems and lead to the possible discovery of other new cascade reactions. As indicated in the reaction path, the key for a successful Michael–Michael–aldol process is to switch the irreversible β-elimination step (**B** to **C**) into an equilibrium, and expect the intramolecular aldol reaction (formation of **G**) to be a new irreversible step under proper reaction conditions. Since the α-proton in the allylic nitro compound, **C**, is acidic, deprotonation of **C** will be one simple approach in converting the **B**–**C** transformation to an equilibrium. The reactions between allylic nitro compounds **1** and strong base KOtBu were then investigated.

As shown in Scheme 2, treatment of a nitroalkene with an enone or α,β-unsaturated ester gave allylic nitroalkane **1** in good yields with the presence of L-proline as a Lewis base. The cyclohexane was not formed under this condition due to the irreversible β-elimination. Reactions of **1** with KOtBu caused the decomposition of **1**, producing the nitroalkene. However, no cyclization product was observed and extension of the reaction time resulted in polymerization of the nitroalkene.



Scheme 2 Decomposition of γ-keto allylic nitro compounds.

Since the base indeed led to the deprotonation of **1**, converting the irreversible elimination to an equilibrium, the fact that no cyclohexane was formed under this reaction may be caused by either the equilibrium in the intramolecular aldol step (**F** to **G**) or the unfavored equilibrium between **A** and **B**. To evaluate these crucial factors that influence the transformation, reactions between **1** and carbonyl-activated alkenes **2** were investigated (Table 1).

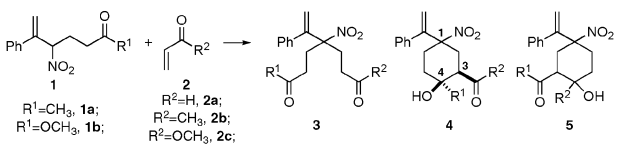
As indicated in Table 1, reactions between **1** and **2** would presumably form three different condensation products: the simple Michael addition product, **3**, the kinetic aldol product, **4**, and the thermodynamic aldol product, **5**.[8] The Michael addition did not occur between **1** and **2** in the absence of the base, even for the most reactive enal, **2a**, in the presence of proline (activation of enal) in DMSO (entries 1–2). Enal polymerization occurred when **2a** was treated with base in DMSO (entry 3). With the addition of a strong base (KOtBu), allylic nitro compound **1** decomposed (entry 5) through the reaction path shown in Scheme 2. With the application of a mild base with **1b** and ester **2c**, the Michael addition product, **3a**, was observed in poor yield (entry 6). However, the desired intramolecular aldol reaction did not occur, which was likely to be due to the poor reactivity of the ester group under the reaction conditions. This result suggested that the Michael–aldol reaction was possible if proper basic conditions were applied (deprotonation of the more acidic nitro carbon hydrogen rather than the carbonyl α-proton). Encouraged by this result, we then investigated the reaction of ketone **1a** with different Michael receptors **2** in the presence of various mild bases. To our pleasure, reactions between **1a** and **2a**/**2b** gave the desired Michael–aldol product **4a**/**4b** in the presence of Et_3N (entries 7–8), although with low reaction rates. The reaction rate for enal **2a** was later improved with the addition of a catalytic amount of proline (entry 9, carbonyl activation). Although NaN_3 and K_2CO_3 could also promote this reaction, Et_3N gave the best results, producing nitro-substituted cyclohexane **4a** in excellent yield.

Notably, the thermodynamic product, **5**, (addition of the ketone α-carbon to aldehyde) was unobserved in all cases (even without proline activation, entry 7).[9] This was also confirmed by the reaction between ester **1b** and enal **2a**, where Michael addition product **3b** was produced in excellent yield and no further cyclization product formed under the reaction conditions (entry 15). Moreover, the aldol product, **4**, was stable under even strong basic conditions: treatment of **4a** with KOtBu at 60 °C showed no decomposition, even after 24 h. All these results strongly suggested that the intramolecular aldol condensation was a rapid irreversible step in this cascade process, which drove the equilibrium into the desired cyclohexane product.

Meanwhile, although three stereogenic centers were generated in product **4**, only two C-1 diastereomers were obtained.[10] This was likely to be caused by the small size difference between the nitro and the vinyl groups on the C-1 position in the chair-like transition state. Various enals were applied to the reactions with allylic nitro compound **1** and the desired nitro-substituted cyclohexanes **4** were obtained with good yields and diastereoselectivity (Table 2).

With these optimal conditions for the intramolecular aldol reaction, we then investigated the direct condensation between nitroalkenes and enones. As expected, the one-pot Michael–Michael–aldol condensation was successfully achieved

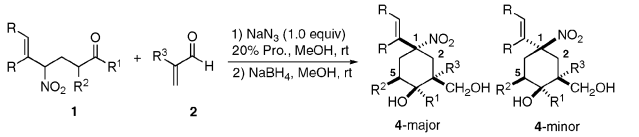
Table 1 Allylic nitro compound Michael–Aldol condensation[a]

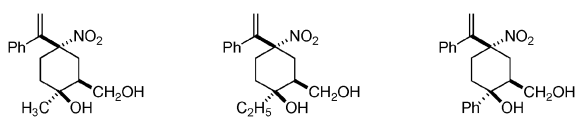


	Sub.		Conditions						
	1	2	Cat. (20%)	Solv.	Base (1.0 equiv.)	Time/h	Conv. (%)[b]	Prod.	dr[c]	Yield (%)[d]
1[e]	**1a**	**2a**	Pro	DMSO	—	48	0	—	—	—
2[e]	**1b**	**2a**	Pro	DMSO	—	48	0	—	—	—
3[e]	**1a**	**2a**	Pro	DMSO	Et_3N	12	<5	n.d.	n.d.	n.d.
4	**1b**	**2c**	—	DMSO	—	48	0	—	—	—
5	**1b**	**2c**	—	THF	KOtBu	20	100	trace	n.d.	trace
6	**1b**	**2c**	—	DMSO	Et_3N	20	10	**3a**	—	8
7	**1a**	**2a**	—	MeOH	Et_3N	20	75	**4a**	2.4:1	68
8	**1a**	**2b**	—	MeOH	Et_3N	20	<5	**4b**	n.d.	<5
9	**1a**	**2a**	Pro	MeOH	Et_3N	5	100	**4a**	2.4:1	90
10	**1a**	**2b**	Pro	MeOH	Et_3N	20	<5	**4b**	n.d.	<5
12	**1a**	**2a**	Pro	MeOH	NaOAc	5	100	**4a**	—	0
13	**1a**	**2a**	Pro	MeOH	NaN_3	5	100	**4a**	2.4:1	86
14	**1a**	**2a**	Pro	MeOH	K_2CO_3	5	100	**4a**	2.3:1	71
15	**1b**	**2a**	Pro	MeOH	Et_3N	5	100	**3b**[f]	—	90

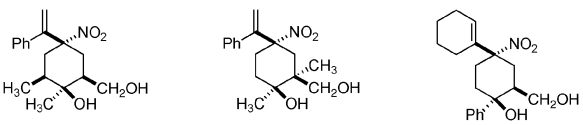
[a] **1** : **2** = 1 : 2, c = 0.2 M. [b] Based on the consumption of **1** by NMR. [c] Based on crude NMR analysis of two C-1 isomers. [d] Isolated yields of all isomers. [e] Polymerization of enal **2a**. [f] Isolated yield of *in situ* reduced alcohol.

Table 2 Cascade Michael–Aldol condensation of **1** and enals[a]





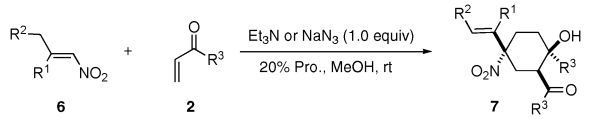
4c: 92%, dr = 3.6 : 1 **4d**: 85%, dr = 3.2 : 1 **4e**: 84%, dr = 3.0 : 1



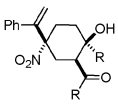
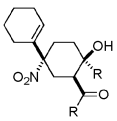
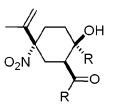
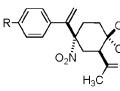
4f: 78%, dr = 4.0 : 1 **4g**: 82%, dr = 2.2 : 1[b] **4h**: 83%, dr = 12 : 1

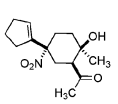
[a] **1** : **2** = 1 : 2, c = 0.2 M; dr values are based on crude ^{1}H NMR analysis; isolated yields of all isomers. [b] The relative stereochemistry was not identified.

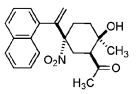
Table 3 Cascade Michael–Michael–Aldol condensation[a]

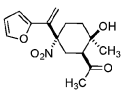


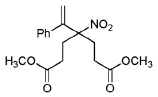
6 2 7

	R	dr[b]	Yield (%)[c]		R	dr[b]	Yield (%)[c]
	CH_3	3.7 : 1	**7a**: 90		CH_3	6.0 : 1	**7d**: 88
	C_2H_5	3.2 : 1	**7b**: 81		C_2H_5	6.4 : 1	**7e**: 88
	C_6H_5	8.2 : 1	**7c**: 82		C_6H_5	14 : 1	**7f**: 82
	CH_3	4.5 : 1	**7g**: 80		CH_3	3.6 : 1	**7j**: 84
	C_2H_5	5.1 : 1	**7h**: 72		NO_2	3.8 : 1	**7k**: 87
	C_6H_5	12 : 1	**7i**: 77		Cl	4.1 : 1	**7l**: 83


7m: 76%, dr = 5.0 : 1


7n: 82%, dr = 4.2 : 1


7o: 76%, dr = 3.0 : 1

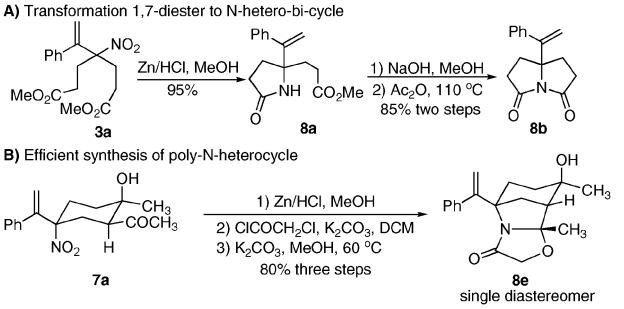

3a: 86%

[a] **1** : **2** = 1 : 4, *c* = 0.2 M, reaction generally finished in 10–20 h. [b] dr determined by crude ^{1}H NMR analysis. [c] Isolated yields of all isomers.

with excellent yield and good diastereoselectivity. The substrate scope is summarized in Table 3.

As shown in Table 3, proline could successfully promote the cascade Michael–Michael–Aldol reaction with the addition of mild bases (Et_3N or NaN_3). Application of an α,β-unsaturated ester gave a good yield of Michael–Michael addition product **3a** without further Dieckmann condensation.[11] The enantioselective intramolecular aldol condensation of 1,7-dialdehyde has been reported with excellent ee using a proline catalyst.[12] However, this cascade transformation gave a very low enantioselectivity (<20% ee).[13] This could be caused by the lack of formation of an H-bond between the proline carboxylate group and carbonyl oxygen under basic conditions. Investigation of different proline derivatives with possible formation of a stronger H-bond is currently undergoing in our group. As functional group-enriched compounds, both **3** and **7** can be readily converted into complex *N*-heterocycles through simple transformations. Two effective derivatizations are summarized in Scheme 3, which further emphasize the strength of the reported method as a highly efficient new approach in complex molecule construction.

In conclusion, a one-pot condensation of nitroalkenes and carbonyl-activated alkenes was developed. The optimal conditions were developed with the application of both Lewis base and mild bases. Through this process, functional group-enriched cyclohexanes were prepared with excellent yields and good diastereoselectivity. The asymmetric transformation and application of this approach in natural product total synthesis are currently under investigation.



Scheme 3 Synthesis of complex *N*-heterocycles from the nitro-substituted 1,7-diesters and cyclohexanes.

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Notes and references

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13 For compounds **4** and **7**, less than 20% ee was observed with L-proline as the catalyst.

