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A Recyclable Organocascade Reaction System: Stereoselective Precipitation of Optically Active *cis*-δ-Lactols with Quaternary Stereocenters during the Michael–Hemiacetalization Reaction

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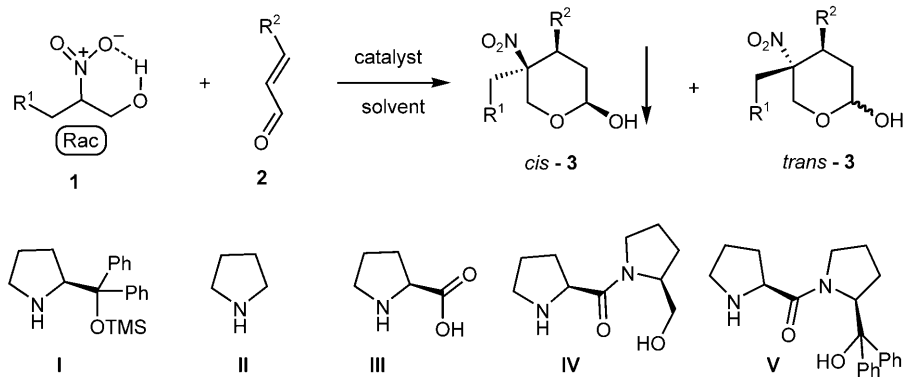
Abstract: A cascade Michael–hemiacetalization reaction between β-substituted β-nitroethanols and α,β-unsaturated aldehydes is described, which provides a convenient and efficient synthesis for *cis*-δ-lactols with quaternary stereocenters in moderate yields with excellent enantioselectivity. Based on the selective precipitation of *cis*-δ-lactols, which were isolated by filtration, the catalytic system in the filtrate can be reused directly and recycled for eight times without any obvious deterioration in enantioselectivity.

Keywords: cascade reaction; green chemistry; hydrogen bonding; organocatalysis; quaternary stereocenters

Since the pioneering works by List, MacMillan and their co-workers in 2000,[1] asymmetric organocatalysis has been widely studied over the past decade[2] and has become a powerful tool for the synthesis of natural products and optically active compounds.[3] As response to the increasing economic and ecological pressure, the development of recyclable organocatalysts has undoubtedly attracted researchers' attention and a number of successful strategies have been reported.[4] Meanwhile, the simplicity of product purification and direct circulation of excess reagents are also very important to improve the sustainability of reaction processes in large-scale industrial production.[5]

Chiral building blocks possessing an N-substituted quaternary stereocenter have important applications in biological, medicinal and synthetic organic chemistry.[6] Consequently, the development of efficient strategies to access these compounds is still a hot research topic, and to date, several organocatalytic methods have been established.[7,8] To the best of our knowledge, however, there is no report describing the asymmetric Michael addition of non-equivalent α,α-dialkyl-substituted nitromethanes to α,β-unsaturated aldehydes, although this transformation is an attractive approach for the stereoselective formation of N-substituted quaternary stereogenic centers. Obviously, the paucity of the transformations is mainly due to their relatively poor reactivity.

We presumed that non-equivalent α,α-dialkyl-substituted nitromethanes **1** would be activated by introducing a hydroxy group into the corresponding β-position in view of the significant role of hydrogen bonding in substrate activation (Scheme 1).[9] Moreover, these transformations can furnish δ-lactols with N-substituted quaternary carbons adjacent to the hydroxy group, which are precursors in the synthesis of natural products[10] and biologically active pharmaceuticals,[11] for example, manzacidins,[10b] dichomitone,[10c] shahamin K,[10d] inhibitors of purine nucleoside phosphorylase[11b] and peptidomimetics.[11c] In addition, this kind of δ-lactol core, as a versatile synthetic platform, can be easily converted to useful products[12] such as δ-lactones, tetrahydropyrans, β-amino alcohols, α- and γ-amino acids. In this communication, we describe one efficient secondary amine-catalyzed cascade reaction involving an initial Michael addition of β-alkyl-β-nitroethanols **1** to α,β-unsaturated aldehydes **2** and a subsequent hemiacetalization.[13] In this process, functional group-rich δ-lactol derivatives **3** were formed with excellent enantioselectivity. More interestingly, a highly stereoselective precipitation of the *cis*-**3** was observed during the reaction, and *cis*-**3**, as a

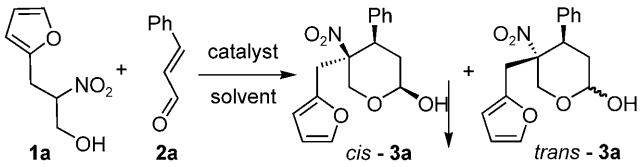


Scheme 1. Synthesis of δ-lactols by a Michael–hemiacetalization cascade process.

single enantiomer, can be easily isolated by filtration from the reaction mixture. Furthermore, the catalyst and excess reagents can be directly reused in the next cycle, which demonstrates the recyclability of the homogeneous organocatalytic system.

The cascade reaction of 3-(furan-2-yl)-2-nitro-1-propanol (**1a**) and cinnamaldehyde (**2a**) was first investigated in chloroform at room temperature, in the presence of different amine catalysts[14] together with co-catalyst benzoic acid (Table 1, entries 1–5). To our delight, the reaction proceeded smoothly and was completed within 24 h. Among these pyrrolidine-based organocatalysts, only diphenylprolinol silyl ether (**I**) gave good enantioselectivity for **3a** (90% *ee*; Table 1, entry 1). The interesting thing is that just *cis*-**3a** selectively precipitated as a single diastereomer during the reaction although the diastereoselectivity of **3a** is moderate in all cases. In fact, *cis*-**3a** can be isolated by filtration with moderate yields, thus avoiding time-consuming chromatographic purification. Subsequently, using **I** as the catalyst and lowering the reaction temperature to 4 °C, our evaluation turned to the solvent and we found that chloroform was the best solvent for the reaction in terms of chemical yields and enantioselectivities (Table 1, entries 6–11). In neat chloroform, **3a** was generated with a 3:1 diasteromeric ratio in an enantiopure form (Table 1, entry 6). Addition of methanol into chloroform led to an obvious decrease both in the diastereomeric ratio and in enantioselectivity (1:1 *dr*; 92% *ee*; Table 1, entry 10), and in methanol, only small amount of **3a** was formed (Table 1, entry 11). To probe the function of the hydroxy group of **1a**, the two similar structures **VI** and **VII** were tested under the same conditions, but no Michael adduct was detected (Scheme 2). In addition, we have analyzed the interaction between the chiral catalyst **I** and **1a** by means of NMR spectroscopy, and confirmed the formation of a tight complex **1a**·**I** (see the Supporting Information, **F**). All these results may suggest that the hydroxy group of **1a** not only acts as an active site to form the δ-lactol and to promote the Michael addition in the cascade system[13q] but also plays a role in enhancing the reactivity of disubstituted nitromethane through intramolecular hydrogen bonding.

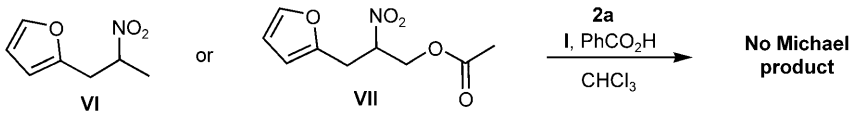
Table 1. Representative screening results of the cascade reaction.[a]



Entry	Catalyst	Solvent	T [°C]/t [days]	Yield [%][b]	dr[c]	ee [%][d]
1	**I**	$CHCl_3$	r.t./1	51/82[e]	2:1	90
2	**II**	$CHCl_3$	r.t./1	47	3:2	–
3[f]	**III**	$CHCl_3$	r.t./1	53	2:1	30
4	**IV**	$CHCl_3$	r.t./1	50	2:1	52
5	**V**	$CHCl_3$	r.t./1	49	2:1	43
6[g]	**I**	$CHCl_3$	4/4	62	3:1	>99
7	**I**	$PhCH_3$	4/4	58	3:1	>99
8	**I**	CH_2Cl_2	4/4	55	2:1	99
9	**I**	CH_3CN	4/4	54	2:1	99
10[h]	**I**	$CHCl_3$	4/4	32	1:1	93
11	**I**	CH_3OH	4/4	<5	–	–

[a] Reactions performed with **1a** (0.30 mmol), **2a** (0.90 mmol), catalyst (0.06 mmol) and benzoic acid (0.06 mmol) in different solvents (0.6 mL).
[b] Isolated yield of *cis*-**3a** by filtration.
[c] Determined by ^{1}H NMR spectroscopy.
[d] The *ee* value of *cis*-**3a**, which was determined by HPLC analysis after conversion to the corresponding δ-lactone.
[e] Isolated yield of **3a** by flash chromatography over silica gel.
[f] No benzoic acid.
[g] In fact, when *cis*-**3a** was isolated by flash chromatography, its *ee* value was determined to be 98%.
[h] CH_3OH (3 mmol) added.

With the optimized reaction conditions in hand, the scope of the organocascade reaction was explored. A wide range of β-substituted β-nitroethanols **1** and α,β-unsaturated aldehydes **2** were tested. As summarized

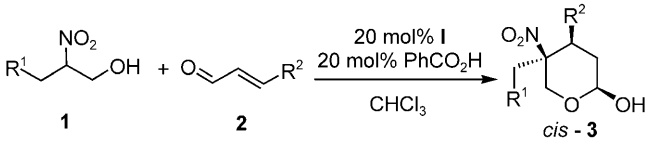


Scheme 2. Reaction of **VI** or **VII** with **2a**.

in Table 2, both electron-donating and electron-withdrawing groups, as well as the substitution patterns on the aryl substituent of **1** and **2** were tolerated. In each case, *cis*-**3** was easily isolated by filtration in good yield (53–79%) and excellent enantioselectivity as detemined by the corresponding δ-lactones (see the Supporting Information). In the case of an aliphatic substituent (e.g., R^1=methyl), no precipitation appeared and a moderate yield of *cis*-**3p** was isolated by flash chromatography over silica gel. Unfortunately, when an aliphatic unsaturated aldehyde like crotonaldehyde was tested, the cascade reaction only gave low yield of the δ-lactol without any precipitation during the reaction.

Encouraged by the results of the reaction scope, the recyclability of the catalytic system was examined on a large scale reaction between **1a** and **2a**. Due to the precipitation of *cis*-**3a** during the reaction, this catalytic system can be reused directly in next cycle only by adding **1a** and **2a** after filtration of *cis*-**3a**. The results shown in Table 3 demonstrate that this catalyt-

Table 2. Reaction of β-substituted β-nitroethanols **1** with **2**.[a]



R^1, R^2	Yield [%][b]	*dr*	*ee*[c] [%]
2-furanyl, C_6H_5	**3a**, 63	3:1	>99
C_6H_5, C_6H_5	**3b**, 54	2:1	>99[d]
4-FC_6H_4, C_6H_5	**3c**, 57	3:1	>99[d]
4-$NO_2C_6H_4$, C_6H_5	**3d**, 79	5:1	99
4-ClC_6H_4, C_6H_5	**3e**, 71	5:1	>99
4-$CH_3OC_6H_4$, C_6H_5	**3f**, 53	3:1	>99[d]
3,4-$(OCH_2O)C_6H_3$, C_6H_5	**3g**, 56	3:1	>99[d]
3-$NO_2C_6H_4$, C_6H_5	**3h**, 73	5:1	>99
2-ClC_6H_4, C_6H_5	**3i**, 69	4:1	>99
4-$NO_2C_6H_4$, 4-$CH_3C_6H_4$	**3j**, 63	3:1	>99
4-$NO_2C_6H_4$, 4-ClC_6H_4	**3k**, 71	5:1	>99
4-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$	**3l**, 53	2:1	>99[d]
4-$NO_2C_6H_4$, 2-FC_6H_4	**3m**, 61	3:1	>99[d]
4-$NO_2C_6H_4$, 3,4-$(OCH_2O)C_6H_3$	**3n**, 63	3:1	>99[d]
4-$NO_2C_6H_4$, 3,4-$(CH_3O)C_6H_3$	**3o**, 59	3:1	96[d]
CH_3, C_6H_5	**3p**, 56[e]	2:1	95
4-ClC_6H_4, CH_3	<10	–	–

[a] Reactions performed using **1** (0.50 mmol), **2** (1.50 mmol), **I** (0.10 mmol) and benzoic acid (0.10 mmol) in chloroform (1.0 mL) for 4 days at 4 °C.
[b] Isolated yield of *cis*-**3** by filtration.
[c] The *ee* value of *cis*-**3**, which was determined by HPLC analysis after conversion to the corresponding δ-lactone.
[d] For 9 days at −20 °C.
[e] Isolated yield by column chromatography.

Table 3. Recycling in the organocascade reaction of **1a** and **2a**.[a]

Cycle	Time [days]	Yield [%][b]	*ee* [%]	Cycle	Time [days]	Yield [%][b]	*ee* [%]
1	5	64	99	5	6	78	99
2	5	76	99	6	7	76	99
3	5	79	99	7	8	77	98
4	5	81	99	8	9	75	98

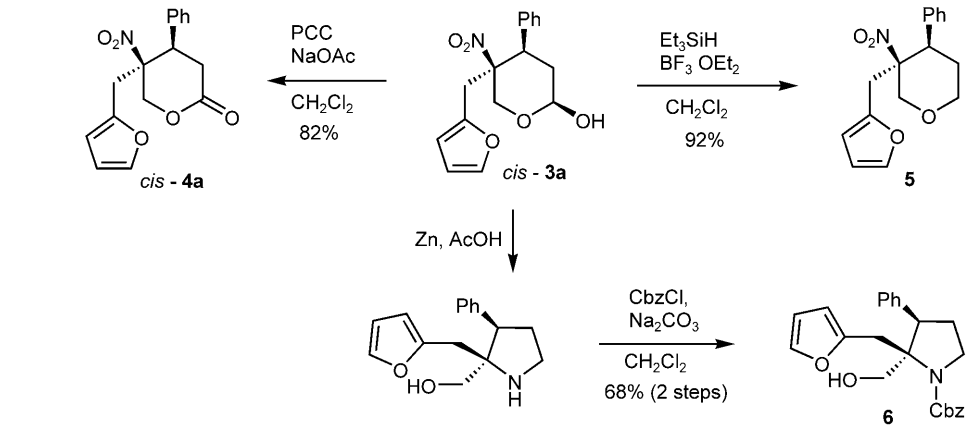
[a] The cascade reaction was carried out using **1a** (10 mmol) and **2a** (30 mmol) with 20 mol% of **I** and 20 mol% benzoic acid in cycle 1, and in cycles 2–8 only **1a** (10 mmol) and **2a** (10 mmol) were added.
[b] Isolated yield of *cis*-**3a** by filtration.

ic system was readily recyclable for eight cycles without obvious deterioration in both enantioselectivity and yield. In the end, *trans*-**3a** was separated from the filtrate with excellent enantioselectivity (98% *ee*) by flash chromatography over silica gel (see the Supporting Information).

Next, the synthetic versatility of the functional group-rich *cis*-δ-lactols **3** has also been explored (Scheme 3). Quaternary δ-lactone *cis*-**4a** and tetrahydropyran **5** could be readily synthesized directly from *cis*-**3a** in 82% and 92% yields, respectively. In addition, reduction of *cis*-**3a** with Zn in AcOH, followed by protection with benzyl chloroformate, provided the quaternary prolinol **6** in 68% total yield *via* two steps.

The absolute configuration of the *cis*-δ-lactol was determined to be 2*S*,4*R*,5*S* by single-crystal X-ray analysis of the compound **5** and NOE analysis of *cis*-**3a** (Figure 1). Unexpectedly, the absolute configuration of the stereocenter bearing the Ph group was opposed to that of the results obtained in other Michael additions of α,β-unsaturated aldehydes to nitroalkanes catalyzed by (*S*)-α,α-diphenylprolinol trimethylsilyl ether **I**.[13m,15]

Furthermore, we have studied the relationship between the enantiomeric excess of δ-lactone *cis*-**4a**, which was derived from the cascade reaction product **3a** by *in situ* oxidation, and the optical purity of the catalyst **I**. The observed results, graphically depicted



Scheme 3. Synthetic transformations of *cis*-**3a**.

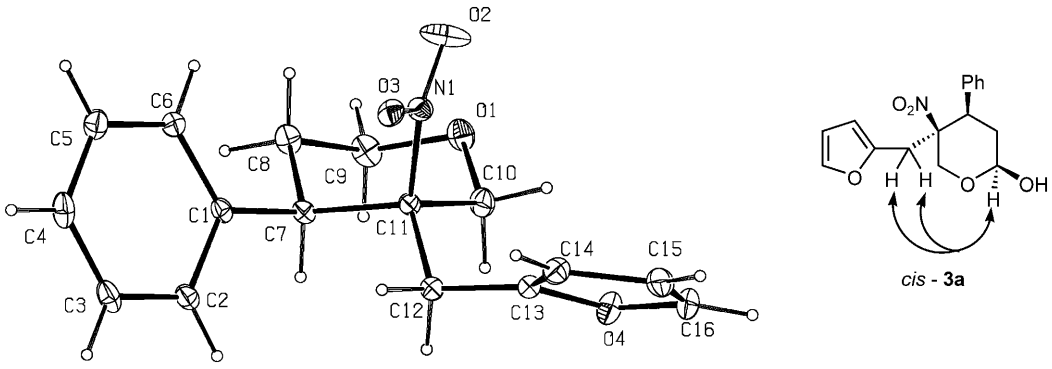


Figure 1. X-ray crystal structure of **5**[16] and results of the NOE measurements of *cis*-**3a**.

in Figure 2, clearly demonstrate a modest, but real, negative non-linear effect.[17] This suggested the possibility that the cascade reaction could proceed through a pathway involving two catalyst molecules in the transition state of the enantioselective step.[18]

In summary, we have developed a reliable and convenient method to access δ-lactols containing quaternary stereocenters *via* an organocascade reaction between α,β-unsaturated aldehydes and β-substituted β-nitroethanols activated by intramolecular hydrogen bonding. The resulting functionalized enantiomerically pure *cis*-δ-lactol with unusual stereochemistry that precipitates stereoselectively during the reaction can be isolated in good yield just by filtration. Furthermore, the catalyst and excess reagents in the filtrate can be reused directly and recycled on a large scale for eight times without deterioration in both enantioselectivity and yield. Chiral δ-lactones, tetrahydropyrans and prolinols with a quaternary stereocenter, which can be easily derived from *cis*-δ-lactols, are of great potential value in the total synthesis of natural products and medicinal chemistry. Therefore, the method presented here has distinct advantages in terms of operational simplicity, the recyclability of catalytic system, and suitability for large-scale industrial production. To elucidate the mechanistic details about the present cascade system, further investigations are ongoing.

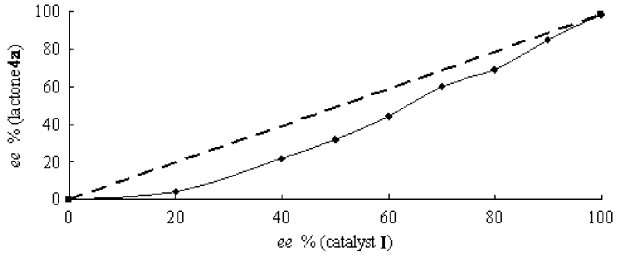


Figure 2. δ-Lactone **4a** *ee* values *versus* catalyst **I** *ee* for the cascade reaction of **1a** with **2a** carried out in $CHCl_3$ at 4 °C. The dashed line represents the expected linear relationship.

Experimental Section

Representative Procedures for the Synthesis of *cis*-3 (Table 2, entry 1)

A vial equipped with a stirring bar was charged with 3-(furan-2-yl)-2-nitro-1-propanol **1a** (0.5 mmol, 85 mg,

1 equiv.), benzoic acid (0.1 mmol, 12 mg, 0.2 equiv.), and neat chloroform (1.0 mL). After addition of cinnamaldehyde **2a** (1.5 mmol, 198 mg, 3 equiv.) and α,α-diphenylprolinol trimethylsilyl ether (0.1 mmol, 33 mg, 0.2 equiv), the reaction mixture was stirred for 4 days at 4 °C. The *cis*-**3a** was isolated and purified by direct filtration/washing with chloroform (0.3 mL); yield: 95 mg (63%). ^{1}H NMR (400 MHz, DMSO): $\delta = 1.65$ (d, $J = 13.2$ Hz, 1H), 2.28 (t, $J = 13.2$ Hz, 1H), 3.24 (d, $J = 15.6$ Hz, 1H), 3.46 (d, $J = 15.6$ Hz, 1H), 3.82 (d, $J = 13.2$ Hz, 1H), 3.80–3.87 (m, 1H), 4.22 (d, $J = 13.2$ Hz, 1H), 5.32 (s, 1H), 6.11 (d, $J = 2.8$ Hz, 1H), 6.36 (s, 1H), 6.60 (d, $J = 2.8$ Hz, 1H), 7.28–7.35 (m, 5H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, DMSO): $\delta = 32.9$, 33.9, 41.6, 62.6, 90.0, 90.1, 109.8, 111.1, 128.0, 128.5, 129.8, 138.7, 143.4, 148.8; HR-MS (ESI): $m/z = 326.09946$, calculated for $C_{16}H_{17}NNaO_5$ $[M+Na]^+$: 326.09989.

Representative Procedures for the Synthesis of *cis*-4

A vial equipped with a stirring bar was charged with *cis*-**3a** (0.2 mmol, 61 mg, 1 equiv.), pyridinium chlorochromate (PCC, 0.3 mmol, 65 mg, 1.5 equiv.), anhydrous sodium acetate (0.6 mmol, 49 mg, 3 equiv.), and 3 mL CH_2Cl_2. The mixture was vigorously stirred at 30 °C for 12 h until the completion of the reaction. Ethyl acetate (5 mL) was then added, the precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The crude lactone product was purified by column chromatography (eluent CH_2Cl_2) to afford *cis*-**4a**; yield: 50 mg (83%); $[\alpha]_D^{11}$: +25.6 (*c* 1.0 in $CHCl_3$); HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 50/50, flow rate = 0.5 mL min^{-1}, $\lambda = 254$ nm): $t_{minor} = 13.48$ min, $t_{major} = 16.93$ min, *ee* 99%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.66$ (d, $J = 16$ Hz, 1H), 2.85 (dd, $J_1 = 18$ Hz, $J_2 = 6.8$ Hz, 1H), 2.94 (dd, $J_1 = 18.2$ Hz, $J_2 = 4$ Hz, 1H), 3.32 (d, $J = 15.6$ Hz, 1H), 4.07 (t, $J = 4.8$ Hz, 1H), 4.49 (d, $J = 14$ Hz, 1H), 4.95 (dd, $J_1 = 14$ Hz, $J_2 = 1.6$ Hz, 1H), 6.04 (d, $J = 3.2$ Hz, 1H), 6.26 (dd, $J_1 = 3.2$ Hz, $J_2 = 2$ Hz, 1H), 7.31 (dd, $J_1 = 6$ Hz, $J_2 = 1.6$ Hz, 3H), 7.40–7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 32.9$, 34.0, 45.0, 68.5, 90.1, 110.0, 110.8, 128.6, 129.1, 129.5, 136.3, 143.1, 146.3, 168.0; HR-MS (ESI): $m/z = 324.08388$, calculated for $C_{16}H_{15}NNaO_5$ $[M+Na]^+$: 324.08424.

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