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Asymmetric organocatalytic Michael–hemiacetalization reaction: access to chiral spiro *cis*-δ-lactones by in situ oxidation of spiro δ-lactols

Mo-Hui Wei [a], Yi-Rong Zhou [a], Liang-Hu Gu [a], Fan Luo [a,*], Fang-Lin Zhang [a,b,*]

[a] School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, 1037 Luoyu Road, Wuhan 430074, China
[b] School of Chemical Engineering, Wuhan University of Technology, 122 Luoshi Road, Wuhan 430074, China

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ABSTRACT

Asymmetric tandem Michael–hemiacetalization reaction between 1-nitromethylcycloalkanol and α,β-unsaturated aldehydes was investigated, which provided an efficient and facile synthesis for spiro *cis*-δ-lactones by in situ oxidation of spiro δ-lactols in good overall yields with high to excellent enantioselectivities and diastereoselectivities.

Natural products containing a spirolactone unit are usually found to exhibit a wide range of biological activities. For examples, drospirenone is a component of certain birth control formulations;[1] gaertneroside is an inhibitor for the activation of the classical pathway of the complement system;[2] and abyssomicin C is a potent antibacterial agent against Gram-positive bacteria.[3] Besides, spirolactones as useful building blocks have already been applied to the total synthesis of bioactive natural products and pharmaceuticals, including variecolin,[4] mevinolin,[5] biyouyanagin A,[6] and (−)-β-vetivone.[7] To date, a variety of synthetic routes have been developed for constructing the spirolactone frameworks,[8] such as dearomatization of phenol to quinine,[9a,b] reductive cross-coupling of ketones with α,β-unsaturated esters,[9c] radical-based approaches,[9d] and furanyl dienolate-based cyclization.[9e] However, few enantioselective approaches to spirolactones have been reported.[9a,b] It is crucial to develop efficient and facile approaches to access highly functionalized spirolactones with high enantioselectivities.

The catalytic asymmetric Michael addition is one of the fundamental bond-forming reactions in organic synthesis. In the past few years, the field of organocatalytic Michael addition has received widespread attention.[10] Among these reactions, the secondary amine-catalyzed asymmetric Michael addition of nitroethanols to α,β-unsaturated aldehydes provides an attractive approach to substituted tetrahydropyran,[11] which could be a useful synthetic intermediate for the synthesis of nitrogen-containing molecules,[12] including substituted δ-lactones, β-amino alcohols, and α-amino acid derivatives. Just recently, we reported a Michael–hemiacetalization reaction of β-substituted β-nitroethanols with α,β-unsaturated aldehydes to afford δ-lactol derivatives bearing N-substituted quaternary carbons with excellent enantioselectivities.[13a] Encouraged by our previous work,[13] we become interested in Michael addition of α-substituted β-nitroethanols to α,β-unsaturated aldehydes, especially, 1-nitromethylcycloalkanols which could provide a facile way for the construction of a spiro carbon after subsequent hemiacetalization (Scheme 1). Here, we describe an efficient Michael–hemiacetalization reaction of 1-nitromethylcycloalkanols **1** and α,β-unsaturated aldehydes **2** to access spiro δ-lactols **3**, and by in situ oxidation, spiro *cis*-δ-lactones **4** were isolated with high to excellent enantioselectivities and diastereoselectivities, as well as in good overall yields.

The tandem reaction of 1-nitromethylcyclohexanol (**1a**) and cinnamaldehyde (**2a**) was first investigated by using 20 mol % of (*S*)-α,α-diphenylprolinol trimethylsilyl ether as a catalyst in the presence of 20 mol % of benzoic acid in CH_2Cl_2 (Table 1, entry 2). The reaction had completed within 24 h and **3a** was obtained almost quantitatively. After oxidization in situ by pyridinium chlorochromate (PCC), *cis*-spirolactone **4a** was isolated in good overall yield. The diastereo- and enantioselectivities of the reaction were respectively determined by ^{1}H NMR and by chiral HPLC after **3a** was oxidized to **4a**. Solvent effects on the above reaction were then examined. Among the solvents listed in Table 1, toluene was the most appropriate one, in which **4a** was obtained with high diastereomeric ratio and enantioselectivity (95:5 dr; 95% ee; Table 1, entry 1). Either dr or ee values of **4a** were decreased to some

* Corresponding authors. Tel.: +86 027 8754 3232; fax: +86 027 8754 3632 (F.L.); tel.: +86 027 8785 0919; fax: +86 027 8785 0919 (F.L.Z.).
E-mail addresses: luofan05@163.com (F. Luo), hyvzfl@gmail.com (F.-L. Zhang).

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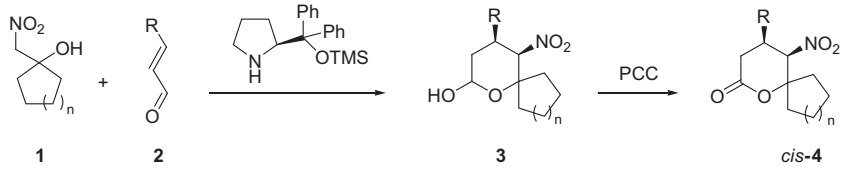
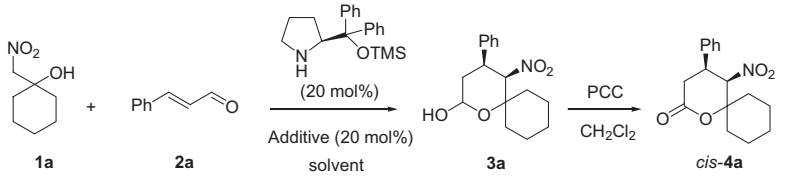


Scheme 1. Synthesis of spiro δ-lactones **4** by Michael–hemiacetalization reaction and in situ oxidation.

Table 1
Optimization of catalytic tandem reaction of 1-nitromethylcyclohexanol with cinnamaldehyde[a]



Entry	Solvent	Additive	*t* (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	$PhCH_3$	PhCOOH	24	82	95:5	95
2	CH_2Cl_2	PhCOOH	24	80	91:9	91
3	$CHCl_3$	PhCOOH	24	80	89:11	90
4	CH_3CN	PhCOOH	24	76	91:9	88
5	CH_3OH	PhCOOH	24	78	90:10	90
6	Et_2O	PhCOOH	24	78	91:9	94
7	THF	PhCOOH	24	79	95:5	92
8	$PhCH_3$	—	36	80	97:3	94
9	$PhCH_3$	CH_3COOH	24	75	95:5	94
10	$PhCH_3$	4-NO_2PhCOOH	24	78	94:6	94
11	$PhCH_3$	Imidazole	14	85	98:2	94
12	$PhCH_3$	DMAP	20	82	93:7	95
13	$PhCH_3$	DABCO	20	80	97:3	93
14	$PhCH_3$	NMM	20	81	97:3	94
15	$PhCH_3$	TEA	20	75	91:9	81
16	$PhCH_3$	DBU	12	82	80:20	0
17[e]	$PhCH_3$	Imidazole	48	85	98:2	96

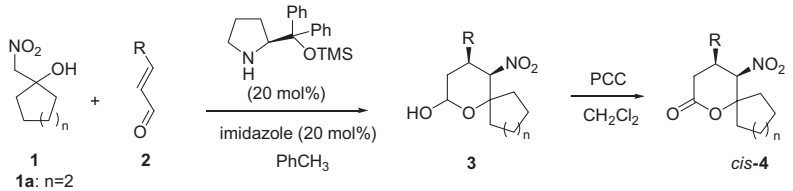
[a] Reactions performed with **1a** (1 mmol), **2a** (0.5 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (0.1 mmol), and additive (0.1 mmol) in indicated solvents (1 mL) at room temperature.
[b] Isolated yield of *cis*-**4a**.
[c] *cis*:*trans* determined by ^{1}H NMR spectroscopy of crude **4a**.
[d] The ee value of *cis*-**4a**, which was determined by chiral HPLC analysis.
[e] Reaction carried out at 4 °C.

extent, when the reaction was performed in other solvents (Table 1, entries 2–7).

Subsequently, the effect of additives was taken into consideration. Some typical acids and bases were tested, and the data are summarized in Table 1 (entries 8–16). When no additive was used, the reaction was accomplished within 36 h and gave 80% yield of *cis*-**4a** with 94% ee. Meanwhile, the dr value was improved to 97:3 which was higher than that obtained in the reaction in the presence of benzoic acid (Table 1, entry 8). This result indicated that acid additive could accelerate the reaction but lower the diastereoselectivity. With slight decline of dr values in the presence of acid additives, however, ee values of the reaction almost kept unchanged. Further evidence was obtained when *p*-nitro benzoic acid was used as a stronger acid additive (Table 1, entry 10). Besides, base additives were also estimated. When imidazole served as the additive, the reaction proceeded much faster and was completed within 14 h; the resulting product *cis*-**4a** was formed in 85% yield with ameliorated diastereomeric ratio (98:2) (Table 1, entry 11). Similar ee and relatively lower dr values were obtained when the reaction was carried out with bases DMAP, DABCO, and NMM (Table 1, entries 12–14). However, in the presence of a strong organic base DBU, both dr and ee values of the reaction declined (Table 1, entry 16). In addition, the ee value of this reaction could be elevated to 96% when reaction temperature was lowered to 4 °C, albeit a prolonged reaction time (48 h) was needed (Table 1, entry 17).

Under the above optimized conditions, the scope of the tandem Michael–hemiacetalization reaction was explored in the presence of 20 mol % of (*S*)-α,α-diphenylprolinol trimethylsilyl ether and 20 mol % of imidazole in toluene at 4 °C. As shown in Table 2, both electron-withdrawing and electron-donating groups on phenyl group were tolerated in the catalytic system (Table 2, entries 1–8). In each case, *cis*-**4** was formed with high to excellent enantioselectivities and diastereoselectivities. However, 3-(furan-2-yl)acrylaldehyde just gave a moderate dr value even at −20 °C (Table 2, entry 9), which might be derived from the different steric hindrance of the different aryl groups. In contrast to our recent results,[13a] the reaction of crotonaldehyde proceeded smoothly and achieved completion within 48 h, although the product *cis*-**4k** was formed with moderate diastereoselectivity and enantioselectivity owning to the less bulky methyl group (Table 2, entry 10). Hex-2-enal was also tolerated in this reaction, furnishing a good yield of *cis*-**4l** with moderate enantioselectivity (Table 2, entry 11). In addition, good yield and high enantioselectivity were obtained for the reaction between 1-nitromethylcyclopentanol (**1b**) and *p*-chlorocinnamaldehyde with 91:9 dr value (Table 2, entry

Table 2
Scope of the reaction between 1-nitromethylcyclohexanols **1** and **2**[a]



1 **1a**: n=2 **1b**: n=1 **2** **3** ***cis*-4**

Entry	**1**	*R*	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	2-ClC_6H_4	73(**4b**)	95:5	98
2	**1a**	3-ClC_6H_4	75(**4c**)	96:4	96
3	**1a**	4-ClC_6H_4	81(**4d**)	95:5	>99
4	**1a**	2,4-diClC_6H_3	74(**4e**)	91:9	93
5	**1a**	2-FC_6H_4	71(**4f**)	91:9	98
6	**1a**	4-$NO_2C_6H_4$	78(**4g**)	98:2	90
7	**1a**	4-MeC_6H_4	73(**4h**)	96:4	92
8	**1a**	4-$MeOC_6H_4$	67(**4i**)	98:2	92
9	**1a**	2-Furanyl	65(**4j**)	79:21	93[e]
10	**1a**	Me	67(**4k**)	86:14	59
11	**1a**	*n*-Pr	63(**4l**)	76:24	72
12	**1b**	4-ClC_6H_4	80(**4m**)	91:9	93

[a] Reactions performed with **1** (1 mmol), **2** (0.5 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (0.1 mmol), and imidazole (0.1 mmol) in $PhCH_3$ (1 mL) at 4 °C for 48 h.
[b] Isolated yield of *cis*-**4**.
[c] *cis*:*trans* determined by ^1H NMR spectroscopy of crude **4**.
[d] The ee value of *cis*-**4**, which was determined by chiral HPLC analysis.
[e] −20 °C for 96 h.

12).The absolute configuration of the spiro *cis*-δ-lactone was determined to be 4*S*,5*R* by single-crystal X-ray analysis of the compound *cis*-**4b**.[14] Furthermore, we have studied the relationship between the enantiomeric excess of spiro *cis*-δ-lactone *cis*-**4a** and the enantiomeric purity of the organocatalyst.[15] Similar results were observed compared to our previous work, which clearly showed a modest negative non-linear effect.[13a]

In summary, we have developed an efficient tandem Michael–hemiacetalization reaction between 1-nitromethylcyclohexanol and α,β-unsaturated aldehydes for the construction of chiral spiro *cis*-δ-lactones by in situ oxidation of spiro δ-lactols, which are potential intermediates for the total synthesis of natural products and pharmaceuticals. The resulting functionalized spiro *cis*-δ-lactones were formed in good overall yields with high to excellent enantioselectivities. Moreover, aliphatic unsaturated aldehydes can also be applied to this tandem reaction providing corresponding products with moderate stereoselectivities.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.039.

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14. The X-ray crystal structure of *cis*-**4b** is presented in Supplementary data.
15. The relationship between *cis*-**4a** ee and organocatalyst ee values is given in Supplementary data.