Tetrahedron Letters 51 (2010) 3827–3829

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Organocatalytic approach to 3,5,6-trisubstituted and 4,6-disubstituted tetrahydropyran-2-ones

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ARTICLE INFO

Article history:
Received 21 April 2010
Revised 17 May 2010
Accepted 18 May 2010

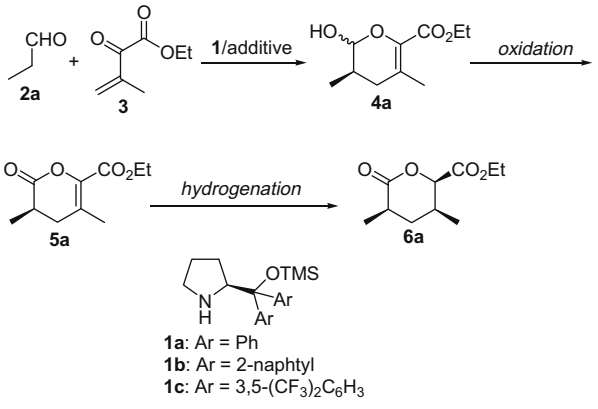
ABSTRACT

The diarylprolinol ether-catalyzed Michael addition and subsequent cyclization of ethyl 3-methyl-2-oxobut-3-enoate with aldehydes, and γ-substituted β,γ-unsaturated-α-ketoesters with acetaldehyde, afforded the corresponding lactals, which were subjected to oxidation and stereocontrolled hydrogenation to provide 3,5,6-trisubstituted and 4,6-disubstituted tetrahydropyran-2-ones with excellent enantioselectivities.

The *syn*-1,3-dimethyl moiety has been frequently found in natural products, particularly the deoxypolyketides.[1] This fact has stimulated numerous investigations for developing new methods to construct functionalized chirons with a *syn*-1,3-dimethyl unit.[2–10] The typical approaches to these building blocks were heavily relied on chiral auxiliary-induced stereoselective enolate alkylations and conjugate additions,[2,3] asymmetric allylic substitution,[2,4] as well as enzymatic resolution of the corresponding *meso*-diols.[5] Recently, some catalytic methods have been developed, which include copper-catalyzed hetero Diels–Alder reaction of (*Z*)-1-ethoxyprop-1-ene with ethyl 3-methyl-2-oxobut-3-enoate,[6] asymmetric carboalumination–vinylation tandem process of styrene,[7] catalytic organocuprate addition of α,β-unsaturated thioesters,[8] enantioselective hydrogenation of polyene compounds[9], and desymmetrization of *meso*-3,5-dimethyl glutaric anhydride.[10]

In the past decade great progress has been achieved in the development of organocatalytic asymmetric reactions, which provide new opportunity for elaborating a variety of chiral building blocks in a more efficient and inexpensive manner.[11] During the investigations on the enamine-based Michael reactions,[12] we became interested in the assembly of *syn*-1,3-dimethyl chiron **6a** by using a cascade Michael addition and cyclization[12b] (or hetero-Diels–Alder reaction as proposed by Juhl and Jørgensen[13]) process. As depicted in Scheme 1, we envisaged that if the reaction of propionaldehyde **2a** and ethyl 3-methyl-2-oxobut-3-enoate **3** proceeded well to afford cyclic semi-acetal **4a** with high enantioselectivity, **6a** could be obtained after oxidation of its semi-acetal unit and subsequent diastereoselective hydrogenation of its C–C double bond. Since its two ester groups are ready for further transformations, this molecule is obviously useful for assembling some known *syn*-1,3-dimethyl building blocks.[2–10]

We initialed our experiment by screening suitable conditions for the organocatalytic reaction of **2a** and **3**. As summarized in Table 1, under our previous conditions,[12b] this reaction completed in 8.5 h, affording **4a** in 92% yield and 90% ee (entry 1). Changing solvent to methanol, DMF, 1,4-dioxane, or THF did not improve the results (entries 2–5). However, better enantioselectivities were observed by using chloroform and toluene as the solvent, although the reaction yields dropped slightly (entries 6 and 7). Switching the catalyst from **1a** to **1b** gave a similar result, but prolonging the reaction time was required (entry 8). When catalyst **1c** was utilized, the reaction turned to be more sluggish (entry 9). Using acids as the additives is beneficial for this reaction, as evident from that a longer reaction time was needed in the absence of the additives (compare entries 6,



Scheme 1.

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doi:10.1016/j.tetlet.2010.05.077

Table 1
Organocatalytic reaction of propionaldehyde **2a** and enone **3** under different reaction conditions[a]

Entry	Solvent	Catalyst/additive	*t* (h)	Yield[b] (%)	ee[c] (%)
1	H_2O	**1a**/$PhCO_2H$	8.5	92	90
2	MeOH	**1a**/$PhCO_2H$	14	85	87
3	DMF	**1a**/$PhCO_2H$	72	63	75
4	1,4-Dioxane	**1a**/$PhCO_2H$	15	77	91
5	THF	**1a**/$PhCO_2H$	72	77	90
6	$CHCl_3$	**1a**/$PhCO_2H$	20	**78**	**96**
7	Toluene	**1a**/$PhCO_2H$	16	72	95
8	$CHCl_3$	**1b**/$PhCO_2H$	33	72	95
9	$CHCl_3$	**1c**/$PhCO_2H$	48	50	97
10	$CHCl_3$	**1a**/—[d]	47	77	89
11	$CHCl_3$	**1a**/AcOH	24	87	88
12	$CHCl_3$	**1a**/AcONa	72	38	94

[a] Reaction conditions: **1** (0.06 mmol), propionaldehyde **2a** (1.2 mmol), enone **3** (0.6 mmol), additive (0.12 mmol), solvent (0. 6 mL), 0 °C for 1 h, and then rt for indicated time.
[b] Isolated yield for **4a**.
[c] Determined by chiral-phase HPLC analysis of **5a**.
[d] No additive was used.

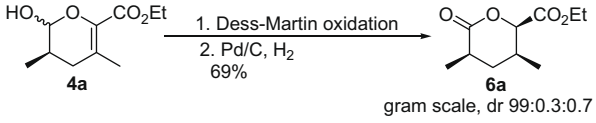
10 and 11). Switching the additives from benzoic acid to acetic acid or sodium acetate led to a decrease in enantioselectivity (entry 11) or yield (entry 12).

After identifying **1a**, benzoic acid, and $CHCl_3$ as the optimized combination, a gram-scale reaction was conducted (Scheme 2). In this case **4a** was isolated with almost the same yield and enantioselectivity. After oxidation of **4a** with Dess–Martin periodinane, we were pleased to observe that Pd/C-catalyzed hydrogenation of **5a** took place in a highly diastereoselective manner. The ratio for **6a** and its two detectable isomers was about 99:0.3:0.7 as determined by GC–MS analysis. The stereochemistry of **6a** was proposed by mechanism analysis and further confirmed by NOESY studies.

Other aldehydes were then examined for synthesizing 3,5,6-trisubstituted tetrahydropyran-2-ones. As shown in Table 2, they all gave the desired products with excellent enantioselectivities. However, diastereoselectivities at the hydrogenation step are slightly different, although the reason is not yet clear.

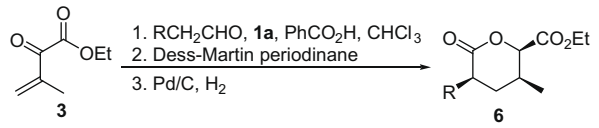
We next explored the possibility of diarylprolinol ether-catalyzed reaction between acetaldehyde and (*E*)-ethyl 2-oxopent-3-enoate **7a**. The purpose for this attempt is to develop a facile route to 4-methyl tetrahydropyran-2-one **10a**. This is a challenging task because some side reactions may occur due to the high reactivity of acetaldehyde as both a nucleophile and an electrophile. Only very recently this special aldehyde was identified as a suitable substrate for organocatalytic asymmetric reactions.[14] To our delight, reaction of **7a** with acetaldehyde proceeded smoothly under the same conditions used for Michael addition of nitroolefins with acetaldehyde by Hayashi et al.[14c] (Table 3, entry 1) and List and co-workers[14d] (entry 2), delivering the desired lactal **8a** with 94–95% ee. However, reaction yields were not satisfactory in these cases. Changing solvent to less polar *n*-hexane and toluene gave similar results (entries 3 and 4). The best result was observed by using chloroform as the solvent (entry 5). Interestingly, introduction of additives led to decrease in reaction yields (entries 6–8).

Oxidation of **8a** with PCC afforded lactone **9a** in 67% yield, which was hydrogenated to give a mixture of **10a** and its *trans*-isomer in a ratio of 5:1. The pure **10a** could be isolated by column chromatography with 49% yield (Table 4, entry 1). Starting from



Scheme 2.

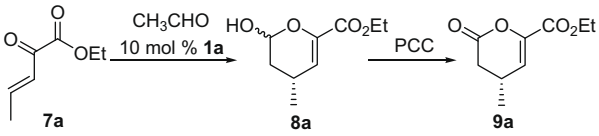
Table 2
Synthesis of 3,5,6-trisubstituted tetrahydropyran-2-ones[a]



Entry	R (product)	Yield[b] (%)	ee[c] (%)	dr[d]
1	Et (**6b**)	48	>99	89:11
2	*n*-Pr (**6c**)	41	99	96:2:2
3	*i*-Pr (**6d**)	29	96	89:7:2:2
4	Bn (**6e**)	30	98	94:6
5	*n*-C_9H_{19} (**6f**)	25	99	98:1.5:0.5

[a] Reaction conditions: **1** (0.06 mmol), aldehyde **2** (1.2 mmol), enone **3** (0.6 mmol), $PhCO_2H$ (0.12 mmol), $CHCl_3$ (0.6 mL), 0 °C for 1 h, and then rt for about 30 h.
[b] Isolated overall yield for three steps.
[c] Determined by chiral-phase HPLC analysis of **5**.
[d] Determined by GC.

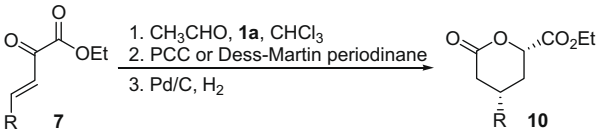
Table 3
Organocatalytic reaction of acetaldehyde and enone **7a** under different reaction conditions[a]



Entry	Solvent	Additive	*t* (h)	Yield[b] (%)	ee[c] (%)
1	1,4-Dioxane	—[d]	45	43	95
2	MeCN	—[d]	17	41	94
3	*n*-Hexane	—[d]	24	52	92
4	Toluene	—[d]	69	44	95
5	$CHCl_3$	—[d]	24	**63**	**96**
6	$CHCl_3$	$PhCO_2H$	12	43	94
7	$CHCl_3$	AcOH	25	43	96
8	$CHCl_3$	AcONa	10	45	96

[a] Reaction conditions: **1** (0.06 mmol), acetaldehyde (6 mmol), enone **7a** (0.6 mmol), additive (0.12 mmol), solvent (0.12 mL), 0 °C for 1 h, and then rt for indicated time.
[b] Isolated yield for **8a**.
[c] Determined by chiral-phase HPLC analysis of **9a**.
[d] No additive was used.

Table 4
Synthesis of 4,6-disubstituted tetrahydropyran-2-ones[a]



Entry	R (product)	Yield (%) 1st/2nd/3rd step[b]	ee[c] (%)	dr[d]
1	Me (**10a**)	63/67/49[e]	96	5:1
2	Ph (**10b**)	64/57/66[e]	97	4:1
3	*i*-Pr (**10c**)	78/55/48[e]	96	4:1
4	*n*-Bu (**10d**)	77/31/56[e]	96	4:1

[a] Reaction conditions: **1** (0.06 mmol), acetaldehyde (6 mmol), enone **7** (0.6 mmol), $CHCl_3$ (0.12 mL), 0 °C for 1 h, and then rt for about 30 h.
[b] Isolated yield.
[c] Determined by chiral-phase HPLC analysis of **9**.
[d] Determined by ^1H NMR.
[e] For pure *cis*-isomer.

different enones, three other 4,6-disubstituted tetrahydropyran-2-ones were assembled in reasonable overall yields (entries 2–4).

In conclusion, we have demonstrated that diarylprolinol silyl ether-catalyzed Michael addition/cyclization cascade reaction of ethyl 3-methyl-2-oxobut-3-enoate with aldehydes, and γ-substituted β,γ-unsaturated-α-ketoesters with acetaldehyde, afforded the corresponding cyclic semi-acetals with excellent enantioselectivities. The simple operation and using cheap reagents and catalyst make these procedures very attractive for large-scale synthesis. After oxidation and stereocontrolled hydrogenation, these products could be converted into 3,5,6-trisubstituted and 4,6-disubstituted tetrahydropyran-2-ones. Among them *syn*-1,3-dimethyl synthon **6a** and ethyl 4-methyl-6-oxo-tetrahydro-2*H*-pyran-2-carboxylate **10a** may find practical applications in natural product synthesis.

Acknowledgments

The authors are grateful to the Ministry of Science and Technology (Grant 2009ZX09501-00), Chinese Academy of Sciences, and National Natural Science Foundation of China (Grant 20632050 & 20921091) for their financial support.

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