Tetrahedron 74 (2018) 3557–3563

Contents lists available at ScienceDirect

Tetrahedron

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

Highly chemo- and enantioselective vinylogous aldol/cyclization cascade reaction to construct chiral 5,6-dihydropyran-2-ones

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ARTICLE INFO

Article history:
Received 26 February 2018
Received in revised form
1 May 2018
Accepted 3 May 2018
Available online 22 May 2018

Keywords:
Asymmetric catalysis
Cascade reaction
Dihydropyranone
Vinylogous reaction
Organocatalysis

ABSTRACT

An organocatalytic chemo- and enantioselective vinylogous aldol/cyclization cascade reaction between β,γ-unsaturated amides and β,γ-unsaturated α-keto esters was developed. With 5 mol% of chiral tertiary amine-thiourea catalyst **C3**, highly functionalized 5,6-dihydropyran-2-ones with a quaternary stereocenter were constructed in a straightforward manner with high yields (up to 99%) and excellent enantioselectivities (up to 98% ee).

1. Introduction

Chiral 5,6-dihydropyran-2-ones are ubiquitous structural motifs in numerous biologically active compounds (Fig. 1).[1,2] For example, tarchonanthuslactone can lower the blood plasma glucose level in diabetic rats,[2b] CI-1029 can inhibit HIV protease,[2c] and Leptomycin B has been used as antifungal antibiotics.[2g] Due to their pharmaceutical importance, great efforts have been devoted to the asymmetric syntheses of chiral 5,6-dihydropyran-2-ones.[3] Among the developed methods, enantioselective catalytic hetero-Diels-Alder reactions[4,5] and vinylogous aldol/cyclization cascade reactions[6–11] are the most efficient to directly construct chiral 5,6-dihydropyran-2-one skeletons. In those reports, the γ-nucleophiles for vinylogous aldol process include α,β-unsaturated carbonyl chloride,[6] α,β-unsaturated aldehydes,[7] olefinic azlactones,[8] β,γ-unsaturated amides,[9] α,β-unsaturated esters with HOBt[10] and 3-alkylidene oxindoles.[11] On the other hand, the previously used aldol acceptors mainly focused on activated isatins, whereas acyclic ketones have been seldom used as vinylogous aldol partners to construct chiral 5,6-dihydropyran-2-ones.[6,7a,7f,8b] Therefore, the development of new electrophiles for the vinylogous aldol/cyclization cascade reaction to construct novel chiral 5,6-dihydropyran-2-ones is still in demand.

β,γ-Unsaturated α-keto esters are a unique class of compounds, which contain both a carbonyl group and an electron-deficient olefin motif.[12] They can act as aldol acceptors[8b,13] as well as Michael acceptors[14] in asymmetric catalysis. The highly chemo- and enantioselectivity of these electrophiles is challenging. Very recently Xu and co-workers[8b] reported an enantioselective vinylogous aldol reaction involving a cascade reaction between olefinic azlactones and β,γ-unsaturated α-keto esters to produce chiral dihydropyranones (Scheme 1a). In previous work,[9] we have developed β,γ-unsaturated amides as γ-nucleophiles for the asymmetric vinylogous aldol/cyclization cascade reaction to form dihydropyranone-containing spiro compounds, and activated cyclic ketones such as isatins and *o*-quinones were used as the electrophiles. These β,γ-unsaturated amides can also react with electron-deficient olefins such as isatylidenes to undergo enantioselective vinylogous Michael/cyclization cascade reaction.[15] With a continuing interest in the asymmetric vinylogous reaction with β,γ-unsaturated amides as γ-nucleophiles, we envisioned that these γ-nucleophiles could react with acyclic partners to construct new chiral 5,6-dihydropyran-2-one compounds by varying the substrates and chiral catalysts. Herein we report a highly chemo- and enantioselective direct vinylogous aldol/cyclization cascade reaction between β,γ-unsaturated amides and β,γ-unsaturated α-keto

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https://doi.org/10.1016/j.tet.2018.05.011
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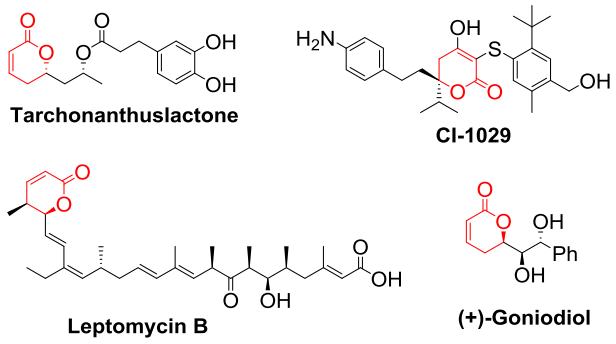
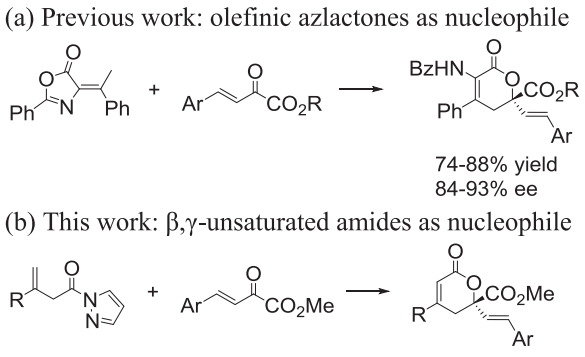


Fig. 1. Examples of biologically active molecules containing chiral 5,6-dihydropyran-2-one skeleton.



Scheme 1. Different approaches to construct chiral dihydropyranone.

esters (Scheme 1b), providing 5,6-dihydropyran-2-ones with a chiral quaternary center.

2. Results and discussion

Initially, a model reaction between β,γ-unsaturated amide **1a** and β,γ-unsaturated α-keto ester **2a** was carried out in dichloromethane at 25 °C to screen the chiral organocatalysts (Fig. 2), and the results are summarized in Table 1. As expected, all these bifunctional organocatalysts provided chiral 5,6-dihydropyran-2-one **3aa** with high enantioselectivities. The tertiary amine-squaramide catalysts **C5** and **C6** displayed lower enantioselectivity than the tertiary amine-thiourea catalysts screened (entries 5 and 6 vs entries 1–4 and 7–9). These results suggest that the H-bonding interaction between the catalyst and the substrate might play an important role in the stereocontrol. Meanwhile, the

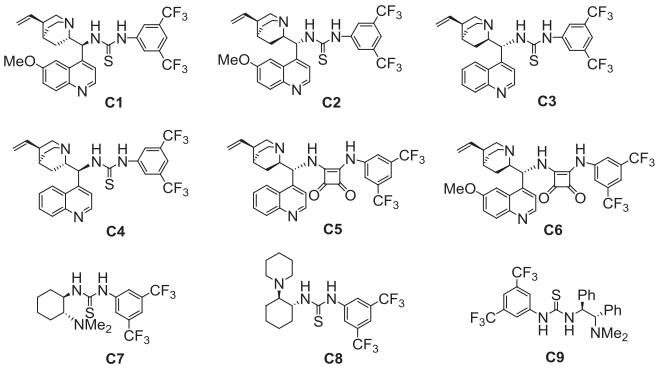
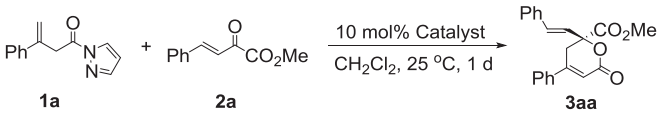


Fig. 2. Structures of the chiral organocatalysts screened.

Table 1
Screening of the chiral organocatalysts for the vinylogous aldol/cyclization cascade reaction[a].



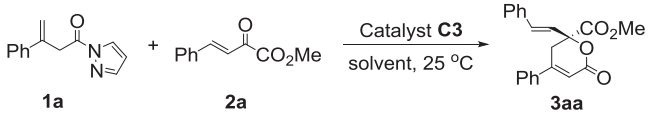
Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**C1**	67	−97
2	**C2**	75	96
3	**C3**	80	96
4	**C4**	67	−96
5	**C5**	88	89
6	**C6**	65	92
7	**C7**	56	96
8	**C8**	71	96
9	**C9**	45	96

[a] The reactions were performed with 0.02 mmol organocatalyst, 0.4 mmol β,γ-unsaturated amide **1a** and 0.2 mmol β,γ-unsaturated α-keto ester **2a** in 1 mL CH_2Cl_2 at 25 °C for 1 day.
[b] Isolated yields after column chromatography.
[c] Determined by chiral HPLC analysis.

chiral backbone of the organocatalysts has a dramatic impact on the chemical yields. Considering the overall chemical yield and the enantioselectivity, tertiary amine-thiourea **C3** was selected as the chiral catalyst for the optimization of reaction conditions (entry 3, 80% yield and 96% ee).

To improve the chemical yield of the cascade reaction, different solvents were surveyed with catalyst **C3** (Table 2, entries 1–9). To our delight, the isolated yields could be increased to 99% with 96%

Table 2
Optimization of reaction conditions [a].



Entry	Solvent	**C3** (mol%)	Time (d)	Yield (%)[b]	ee (%)[c]
1	toluene	10	1	99	96
2	paraxylene	10	1	87	95
3	CH_2Cl_2	10	2	80	96
4	Et_2O	10	1	99	96
5	THF	10	2	70	95
6	EtOAc	10	1	77	95
7	CH_3CN	10	2	75	95
8	CH_3OH	10	2	64	84
9	DMSO	10	2	26	75
10[d]	toluene	10	1.25	99	96
11[e]	toluene	10	0.5	99	95
12	toluene	5	1	99	95
13	toluene	2	2	91	96
14[f]	toluene	5	1	91	96
15[g]	toluene	5	1	99	96
16[g, h]	toluene	5	3	66	95
17	Et_2O	5	1.5	96	94

[a] Unless stated otherwise, the reactions were performed with organocatalyst **C3**, 0.4 mmol β,γ-unsaturated amide **1a** and 0.2 mmol β,γ-unsaturated α-keto ester **2a** in 1 mL solvent at 25 °C.
[b] Isolated yields after column chromatography.
[c] Determined by chiral HPLC analysis.
[d] The reaction was performed at 0 °C.
[e] The reaction was performed at 40 °C.
[f] The reaction was performed in 2 mL toluene.
[g] The reaction was performed in 0.67 mL toluene.
[h] The amount of β,γ-unsaturated amide **1a** was 0.2 mmol.