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Highly chemo- and diastereoselective synthesis of substituted tetrahydropyran-4-ones via organocatalytic oxa-Diels–Alder reactions of acyclic α,β-unsaturated ketones with aldehydes

Liang-Qiu Lu [a], Xiao-Ning Xing [a], Xu-Fan Wang [a], Zhi-Hui Ming [a], Hong-Mei Wang [a,b], Wen-Jing Xiao [a,*]

[a] *Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, Hubei 430079, PR China*
[b] *Beijing Institute of Pharmaceutical Chemistry, Beijing 102205, China*

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Abstract

The first organocatalytic oxa-Diels–Alder reaction of acyclic α,β–unsaturated ketones with aldehydes is described. This reaction represents a highly chemo- and diastereoselective synthesis of substituted tetrahydropyran-4-ones in good yields with dr up to >95:5.
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Substituted di- and tetrahydropyran rings are frequently occurring structural motifs in biologically active natural products.[1] The oxa-Diels–Alder (ODA) reaction is a valuable method for the construction of six-membered oxygen-containing ring systems.[2] Many Lewis acid catalysts have been well established for this particular transformation,[3] while Brønsted acid, for instance, hydrogen bonding has been also developed as a mode of activation for the ODA reaction.[4] However, only a few active dienes, such as Danishefsky's diene[5] and Brassard's diene,[6] are used as the substrates in most cases. Recently, Barbas and co-workers[7a] reported amine catalyzed self-cycloaddition[7b] of α,β-unsaturated ketones, their direct Diels–Alder reaction with nitro olefins,[7c] and Knoevenagel–Diels–Alder reaction.[7d–f] Critical to the success of this strategy involved in situ generation of 2-amino-1,3-butadienes with amine catalyst providing for the synthesis of cyclohexanone derivatives. Utilizing the similar benign fashion, Yamamoto et al.[8a,b] and Córdova[8c] have also developed the organocatalytic asymmetric hetero-Diels–Alder (HDA) reactions using cyclic α,β-unsaturated ketones with nitroso compounds and imines as dienophiles, respectively. However, to the best of our knowledge, there is no organocatalytic HDA reaction yet involving acyclic α,β-unsaturated ketones probably due to the favored formation of the trans acyclic dienes, which is disadvantageous for the progress of the HDA reaction. Accordingly, the exploration of such reaction between acyclic α,β-unsaturated ketones with aldehydes should provide new protocol toward selective synthesis of biologically important tetrahydropyran rings.

Recently, we have reported that chiral secondary amine catalysts can react with ketones or aldehydes forming enamines intermediate, which can be exploited as nucleophiles in aldol[9a–d] and Michael reactions,[9e,f] or imines intermediates to realize inter- and intramolecular Friedel–Crafts reactions.[9g,h] Based on the mechanism of amine catalysis, we envisioned that enamines generated from α,β-unsaturated ketones and amine would act as dienes

* Corresponding author. Tel./fax: +86 27 67862041.
E-mail address: wxiao@mail.ccnu.edu.cn (W.-J. Xiao).

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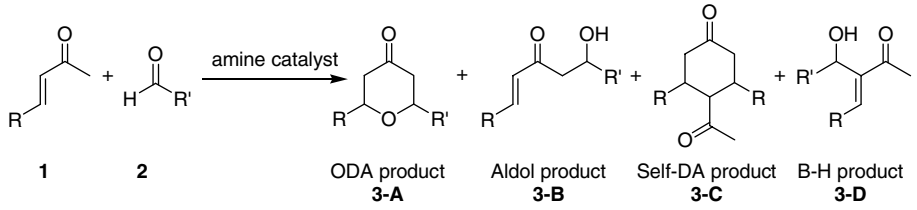
and undergo ODA reactions with aldehydes. Herein, we demonstrate the first organocatalytic ODA reaction of acylic α,β-unsaturated ketones with aldehydes for the construction of six-membered oxa-heterocycles.

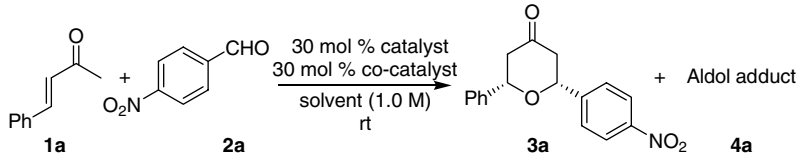
Considering the possible side reactions between α,β-unsaturated ketones with aldehydes catalyzed by amine, for example, aldol reaction, self-DA reaction of α,β-unsaturated ketones, and Baylis–Hillman reaction (Scheme 1), we initially studied a variety of parameters for the reaction of α,β-unsaturated ketones with aldehydes to provide tetrahydropyran derivatives by the ODA approach. Some selected results are shown in Table 1.

Application of pyrrolidine and HOAc as the ODA reaction catalytic system (Table 1) was firstly studied by mixing **1a** (2.5 mmol) with **2a** (0.5 mmol) and pyrrolidine (0.15 mmol), HOAc (0.15 mmol) in dichloromethane (0.5 mL) at room temperature. Fortunately, the *syn* ODA product **3a** (Scheme 2) was obtained in 65% isolated yield after 24 h when the full conversion of **2a** was observed by ^{1}H NMR (Table 1, entry 1), with dr (*syn*/*anti*) = 90:10 and ODA/aldol product = 87:13. However, when other amines, such as dibenzylamine, morpholine, and piperidine were used as the catalyst, the reaction proceeded much more slowly with decreased diastereoselectivities or chemo-selectivities (Table 1, entries 2–4). Variation in co-catalysts,[9,10] Brønsted acid, of pyrrolidine catalyst was next investigated and we found that this changing had a very pronounced effect on the reaction (Table 1, entries 1, 6–8). As can be seen from Table 1, weak acid, such as HOAc, $PhCO_2H$ can effectively promote the ODA reaction, while stronger acid, $NCCH_2CO_2H$, showed somewhat poorer results. No reaction happened when very strong acid HCl was used. Notably, without any acid, a slight decrease in the chemo- and diastereoselectivities was observed though with comparable conversion (Table 1, entries 1 vs 5). Presumably, the tautomerization of enamine and imine intermediates may be sensitive to the nature of acid that are crucial to the ODA reaction. When strong acid was employed as the co-catalyst, the conjugated imine intermediate might be dominant,[9g] which was detrimental to both ODA and aldol reactions. After further examination of the solvents, dichloromethane was the best of choice in terms



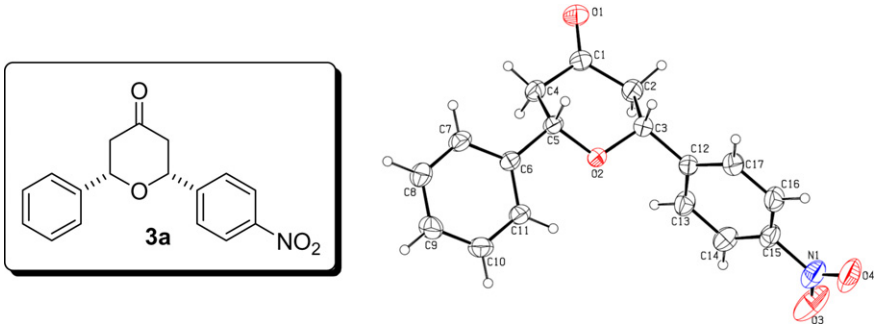
Scheme 1. Envisaged oxa-Diels–Alder reactions and possible side reactions of α,β-unsaturated ketones with aldehydes.

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Co-catalyst	Solvent	Conv.[b]	**3a**/**4a**[b]	dr (*syn*/*anti*)[b]
1	Pyrrolidine	HOAc	CH_2Cl_2	>99	87:13	90:10
2	Bn_2NH	HOAc	CH_2Cl_2	<5	ND[c]	ND[c]
3	Morpholine	HOAc	CH_2Cl_2	31	79:21	81:19
4	Piperidine	HOAc	CH_2Cl_2	40	90:10	73:27
5	Pyrrolidine	No acid	CH_2Cl_2	97	85:15	84:16
6	Pyrrolidine	$PhCO_2H$	CH_2Cl_2	99	71:29	90:10
7	Pyrrolidine	$NCCH_2CO_2H$	CH_2Cl_2	44	70:30	75:25
8	Pyrrolidine	HCl	CH_2Cl_2	<5	ND[c]	ND[c]
9	Pyrrolidine	HOAc	DMF	84	69:13	68:32
10	Pyrrolidine	HOAc	*i*-BuOH	98	62:38	81:29
11	Pyrrolidine	HOAc	$CHCl_3$	92	76:24	83:17
12	Pyrrolidine	HOAc	THF	99	71:29	83:17
13	Pyrrolidine	HOAc	Toluene	99	77:23	82:18

[a] All reactions were carried out using 1 equiv of **2a**, 5 equiv of **1a** in the presence of 30 mol % of catalyst and 30 mol % of co-catalyst in 0.5 mL of solvent at room temperature, 24 h.
[b] Determined by ^{1}H NMR.
[c] Not determined.



Scheme 2. The related configuration of product **3a** determined by X-ray.[11]

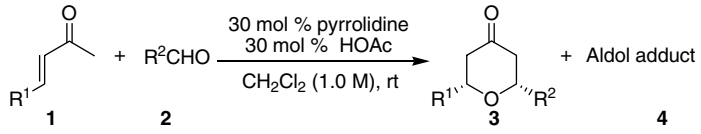
of selectivity and reaction efficiency. So, we chose the following parameters for the highly chemo- and diastereoselective ODA reaction of α,β-unsaturated ketones with aldehydes: pyrrolidine as catalyst, HOAc as co-catalyst and dichloromethane as reaction medium.

Under the optimal reaction conditions, the scope of the ODA reaction was examined with a number of α,β-unsaturated ketones and aromatic aldehydes. As presented in Table 2, pyrrolidine and HOAc catalyzed the reactions between **1** and **2** efficiently to provide the substituted tetrahydropyran-4-ones derivatives **3**. All reactions shown in Table 2 gave the desired ODA products as the major products with high chemo- and diastereoselectivities. Significantly, the ODA adducts and Aldol adducts can be easily separated by column chromatography. However, this strategy was limited to activated aromatic aldehydes, such as *p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde, *m*-nitrobenzaldehyde, and *p*-cyanobenzaldehyde (Table 1, entries 1–4).[12] For the α,β-unsaturated ketones, both aromatic and aliphatic ketones with electronic and steric variations are well tolerated in this reaction.

Based on the above observation and related literatures,[7,8a–c] a possible mechanism was proposed to account for the chemoselectivity of the reaction (Scheme 3). The pyrrolidine catalyst reacts first with α,β-unsaturated ketone **1** to form diene **A**, which then is attacked by **2** affording activated iminium salt **B**. The oxygen anion of the iminium salt **B** undergoes the subsequent cyclization to furnish the corresponding six-membered oxygen-containing ring **C**, while competitive aldol reaction proceeds if the oxygen anion captures a proton before it attacks the β-position of conjugated iminium salt **B**. The ODA adduct is obtained after hydrolysis and the pyrrolidine is released for the next catalytic cycle. The high syn-selectivity was ascribed to the lower energy of transition state when both subsititutes are in e-position.

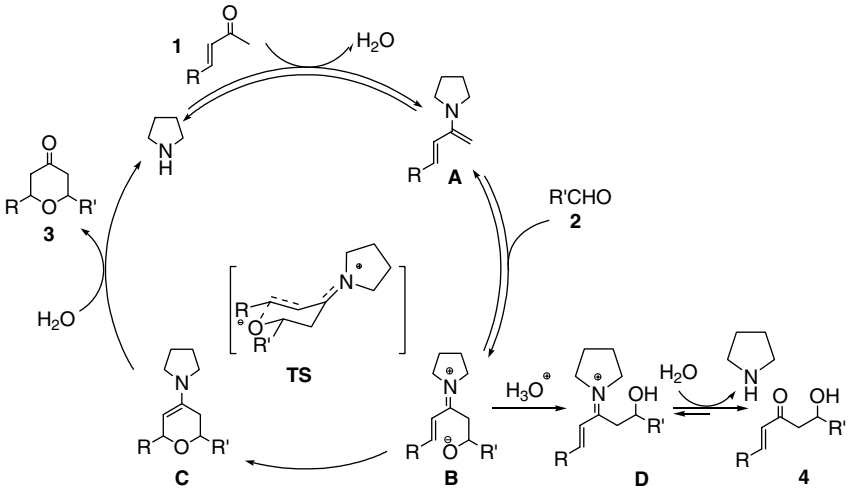
Finally, an attempt to carry out the organocatalytic asymmetric version of this reaction has also been tried. The bifunctional organocatalyst 5, originally developed for enantioselective Aldol reactions of ketones,[9a–d] was employed in the reaction of **1a** and **2a** (Scheme 4). The reaction gave promising results with 45% yield, 77:23 dr,

Table 2
Organocatalytic oxa-Diels–Alder reaction of α,β-unsaturated ketones and aldehydes[a]

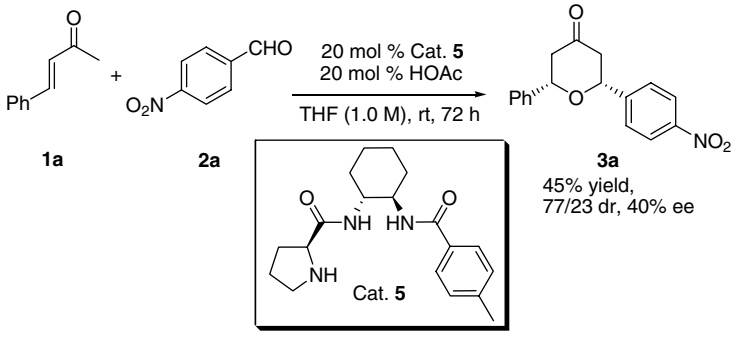


Entry	R^1	R^2	Time (h)	**3/4**[b]	Yield[c] (%)	dr (*syn*/*anti*)[b]
1	Ph (**1a**)	*p*-NO_2–Ph (**2a**)	24	87:13	65 (**3a**)	90:10
2	Ph (**1a**)	*o*-NO_2–Ph (**2b**)	24	93:7	62 (**3b**)	95:5
3	Ph (**1a**)	*m*-NO_2–Ph (**2c**)	24	>95:5	67 (**3c**)	92:8
4	Ph (**1a**)	*p*-NC–Ph (**2d**)	96	>95:5	78 (**3d**)	94:6
5[d]	*p*–NO_2–Ph (**1b**)	*p*-NO_2–Ph (**2a**)	24	85:15	66 (**3e**)	92:8
6	*p*-Cl–Ph (**1c**)	*p*-NO_2–Ph (**2a**)	21	91:9	55 (**3f**)	93:7
7	*p*-Br–Ph (**1d**)	*p*-NO_2–Ph (**2a**)	24	94:6	65 (**3g**)	93:7
8	*m*-Br–Ph (**1e**)	*p*-NO_2–Ph (**2a**)	24	>95:5	69 (**3h**)	92:8
9	*p*-MeO–Ph (**1f**)	*p*-NO_2–Ph (**2a**)	21	>95:5	80 (**3i**)	>95:5
10	C_6H_{11} (**1g**)	*p*-NO_2-Ph (**2a**)	21	95:5	56 (**3j**)	95:5

[a] All reactions were carried out using 1 equiv of aldehyde, 5 equiv of α,β-unsaturated ketone in the presence of pyrrolidine (30 mol %) and HOAc (30 mol %) in 0.5 mL of CH_2Cl_2 at room temperature.
[b] Determined by ^1H NMR.
[c] Isolated yield.
[d] Reaction was carried out in THF.



Scheme 3. Proposed mechanism for the pyrrolidine catalyzed oxa-Diels–Alder reaction.



Scheme 4. Asymmetric catalytic oxa-Diels–Alder reaction of **1a** and **2a**.

and 40% ee of the cis isomer. Attempts to carry out this asymmetric ODA reaction with L-proline as the catalyst were unsuccessful.

In summary, we have demonstrated for the first time organocatalyzed ODA reaction of acyclic α,β-unsaturated ketones with aldehydes to generate substituted tetrahydropyran rings. High chemo- and diastereoselectivities were obtained by the use of pyrrolidine and HOAc as the organocatalysts.[13] Further studies on the chiral amine catalyzed asymmetric ODA reactions are underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.025.

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11. Single crystal X-ray diffraction data for **3a** at 292 K on a Bruker Smart Apex Area CCD equipped with Mo Kα radiation ($\lambda = 0.71073$ Å). Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 638439. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).
12. When active aliphatic aldehydes, such as 2,2,2-trichloro-acetaldehyde and ethyl glycoxylic acid were used, only aldol adducts were isolated as the main products.
13. Representative procedure: α,β-unsaturated ketone **1a** (2.5 mmol), pyrrolidine (0.15 mmol), and HOAc (0.15 mmol) were stirred in 0.5 mL dichloromethane for 30 min at room temperature. Aldehyde **2a** (0.5 mmol) was added and the mixture was then stirred until the completion of the reaction (monitored by TLC). The crude mixture was purified to give oxa-Diels–Alder adduct **3a** through flash column chromatography on silica gel (hexane/ ethyl acetate = 6:1). **3a**: pale yellow solid. ^{1}H NMR δ 8.25 (d, $J = 8.8$ Hz, 2H), 7.64 (d, $J = 8.8$ Hz, 1H), 7.48–7.36 (m, 5H), 4.98 (dd, $J_1 = 12$ Hz, $J_2 = 2.4$ Hz, 1H), 4.88 (dd, $J_1 = 10.4$ Hz, $J_2 = 4.4$ Hz, 1H), 2.80–2.60 (m, 4H); ^{13}C NMR δ 204.7, 147.6, 147.4, 140.0, 128.7, 128.3, 126.3, 125.5, 123.8, 78.9, 77.6, 49.3, 49.1. MS: $m/z = 297.1$. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.59; H, 5.07; N, 4.75. Found: C, 68.68; H, 5.09; N, 4.71. The enantiomeric excess was determined by HPLC (Chiralpak OD column, hexane/ *i*-PrOH 80:20, flow rate 1 mL/min; $t_{minor} = 31.8$ min; $t_{major} = 41.3$ min, $\lambda = 254$ nm).