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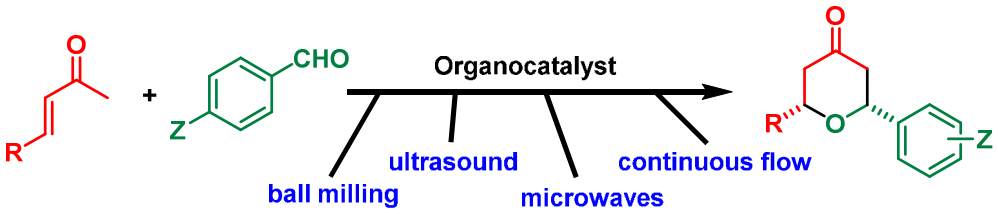
Organocatalytic oxa-Diels-Alder reaction of α,β-unsaturated ketones under non-classical conditions

Melinda Mojzesová, Mária Mečiarová, Roger Marti, and Radovan Šebesta*

Graphical abstract:



Text:

Non-classical activation techniques improve organocatalysed oxa-Diels-Alder reaction of aldehydes with enones.

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Organocatalytic oxa-Diels-Alder reaction of α,β-unsaturated ketones under non-classical conditions

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Non-classical reaction conditions are compatible with organocatalysis and can often improve reaction course. Oxa-Diels-Alder reaction of acyclic α,β-unsaturated ketones with aldehydes is a challenging transformation, which affords valuable pyranone products. Application of microwave irradiation and solvent-free conditions during ball-milling had the best influence on this reaction, in terms of shortening reaction times and increased product yields. Other techniques, such as aqueous conditions, ultrasound and flow conditions also bring notable improvements. Unfortunately, a range of chiral organocatalysts provided only small enantioselectivity of the reaction of up to e.r. 63:37.

Introduction

Asymmetric oxa-Diels-Alder (oxa-DA) reactions using carbonyl compounds as dienes or dienophiles are an effective tool for the synthesis of chiral pyran derivatives.[1,2] A variety of activation modes has been described for this transformation.

Hydrogen-bonding catalysts, such as TADDOL[3,4] or BAMOL[5] efficiently promoted reactions of Rawal´s diene with aromatic aldehydes. These catalysts also served in oxa-DA reaction of Chan´s diene with aldehydes.[6,7,8] TADDOLs activated aldehydes also in hetero-Diels-Alder reactions with Brassard´s[9] and Danishefsky´s dienes.[10]

The reactions of Danishefsky´s diene with 2-oxoacetaldehydes and 2-oxopropanoates were catalysed with chiral bis(sulfon)amides.[11,12] In contrast to TADDOL, these amides activated the carbonyl groups through two hydrogen bonds. High yields and enantiomeric purities of 2-arylpyranones were achieved in reactions of Rawal´s diene with aromatic aldehydes using oxazolyl sulfonamides.[13] Chiral thiourea-catalysed the oxa-DA reaction of cyclic ketones with unsaturated α-oxoesters gave bicyclic products with three stereocentres.[14]

Jørgensen described the first oxa-DA reaction using an enamine activation of aldehydes.[15] Chiral pyrrolidines catalysed the reaction of unsaturated α-oxoesters. The corresponding 2-oxopyran-6-carboxylates were isolated in high yields and with up to 92% ee. Chiral enamines acted as dienophiles in the hetero-DA reaction with α-oxo-β,γ-unsaturated phosphonates.[16] The oxa-DA reaction of *ortho*-quinones and aldehydes afforded chiral benzo[1,4]dioxins.[17]

Oxa-DA reaction of α-chloroaldehydes, as precursors of dienes, with α,β-unsaturated ketones was catalysed with chiral carbenes.[18,19] Carbenes also promoted oxa-DA reactions of ketenes with α,β-unsaturated ketones to give chiral lactones[20] or coumarins.[21]

Chiral tertiary amines catalysed the formation of lactones[22] and tricyclic benzopyrones.[23] Highly diastereo- and enantioselective formal hetero-DA reactions of enones with isatins, which afforded the corresponding spiro oxindole tetrahydropyranones.[24]

Reactivity of α,β-unsaturated ketones in the oxa-DA reaction is considerably lower than that of aldehydes. Xiao described the first asymmetric oxa-DA reaction of aldehydes with α,β-unsaturated ketones, which were activated through dienamines.[25] The best yields were achieved with pyrrolidine as the catalyst, but with chiral catalysts, the yields decreased and enantioselectivity was only 40% ee. Better results were achieved with more reactive trifluoromethyl α,β-unsaturated ketones and aliphatic aldehydes catalysed by chiral prolinol silyl ether.[26]

With regards to the fact, that oxa-DA reactions of simple α,β-unsaturated ketones with aldehydes have been described just once until now[25] and suffer from long reaction time and mediocre yields and selectivities, we decided to study the reaction of enones with aromatic aldehydes under various non-classical reaction conditions. Herein, we describe oxa-DA reactions under microwave irradiation, ultrasound, aqueous

conditions, ball-milling and in a flow microreactor. A variety of chiral organocatalysts has been also evaluated. Pyrrolidine based catalysts **C1**-**C7** were tested, based on their ability to form enamines (Fig. 1).[27]

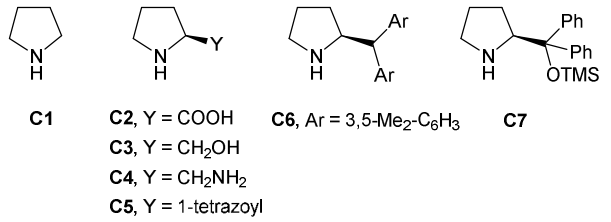


Fig. 1 Pyrrolidine-based organocatalysts used in this study.

We have also screened several hydrogen-bond donating catalysts **C8**-**C15** as they are known to activate carbonyl groups (Fig. 2).[28]

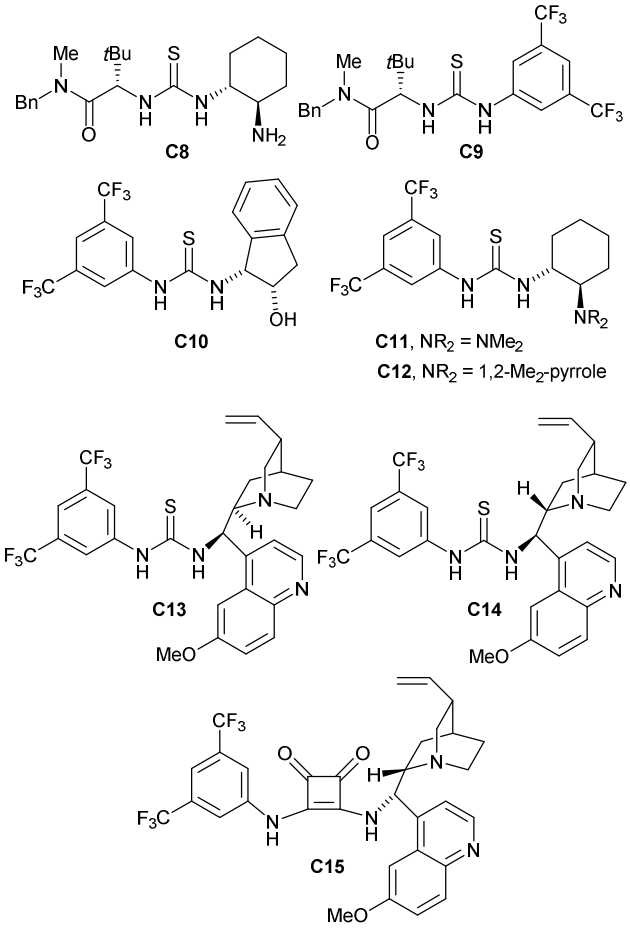
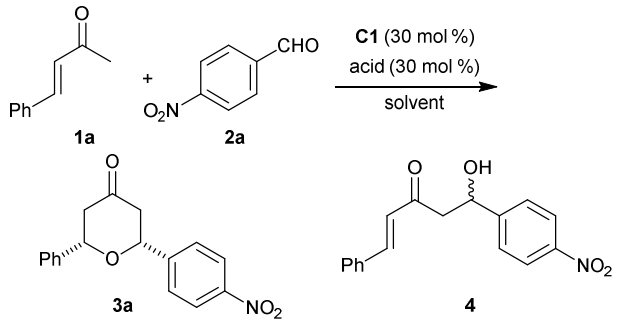


Fig. 2 Structures of hydrogen-bonding catalysts used in this study.

Results and discussion

We started the study with the oxa-Diels-Alder reaction of (*E*)-4-phenylbut-3-en-2-one (**1a**) with 4-nitrobenzaldehyde (**2a**) using pyrrolidine (**C1**) as a catalyst (Scheme 1). The corresponding pyranone product **3a** was obtained in all cases as *syn*-isomer with *syn/anti* ratio ≥ 95:5.



Scheme 1.

When the reaction proceeded in CH_2Cl_2 with AcOH as an additive at room temperature for 48 h, the product **3a** was obtained in 65% yield. Considerable rise of reaction rate was observed at 50 °C. The product **3a** was isolated in 45% yield after 2 h (Table 1, entries 1, 2).

It is well known that an ultrasonic irradiation accelerates a number of organic reactions as a result of extreme temperatures and pressures, which originate during cavitation.[29] Furthermore, Diels-Alder reactions have large negative changes in volume of activation[30] and thus often proceed better under high pressure. Therefore, we carried out the reaction of enone **1a** with aldehyde **2a** in an ultrasonic cleaning bath. Sonochemical reaction (5.5 h, temperature of the bath was 52°C at the end of the experiment; internal temperature 35°C) provided pyranone **3a** in 69% yield (Table 1, entry 3). Chlorinated solvents are not ideal for sonochemical reactions because of possible carbene formation. However, our reaction proceeded without problems. Probably our conditions were not harsh enough to produce any appreciable amount of highly reactive carbene species. When we used water as a solvent, the reaction under classical conditions provided only 29% of product **3a**, which was accompanied by 22% of the product of an aldol reaction **4**. The reaction in water under ultrasonic irradiation gave product **3a** in higher, 50% yield. Interestingly, the product of the aldol reaction **4** was isolated in lower yield (15%) (Table 1, entries 4 and 5). The product **3a** was attained in 46% yield, when toluene was used as a solvent under classical stirring at room temperature for 72 h (Table 1, entry 6). The reaction of enone **1a** with aldehyde **2a** at the same conditions gave a complex mixture of products, when it was performed in methanol. Similarly, a complex mixture of products, comprising a product of α,β-unsaturated ketone, Baylis-Hillman reaction, was obtained, when (*S*)-proline (**C2**), **C5** and **C7** were used as catalysts in CH_2Cl_2 under classical conditions (72 h, r.t.).

We have explored an influence of microwave irradiation (MWI) on the oxa-DA reaction of enone **1a** with aldehyde **2a** (Table 1). The experiments under MWI in a closed vessel in low boiling solvent, such as CH_2Cl_2 at 50 °C for 2 h gave the product **3a** in 45% yield (Table 1, entry 7). On the other hand, the reaction in higher boiling toluene under microwave irradiation proceeded well already at 40 °C. In just 2 h under these conditions, 94% conversion of the aldehyde was observed. The conversion of aldehyde **2a** increased to 97%,

when the reaction was performed at 50 °C for 50 min (Table 1, entries 8 and 9). The cycloadduct **3a** was the only product of the reaction. Further increase of the reaction temperature to 60–80 °C resulted in a complex mixture of products, both in CH_2Cl_2 as well as in toluene. Oxa-Diels-Alder reaction under MWI with chiral catalysts, such as **C3**, or thiourea derivatives did not proceed.

Mechanochemical activation during ball milling usually increases reaction rates due to higher reactant concentrations and more effective inter-molecular contacts.[31] Therefore, we have examined the oxa-DA reaction of the ketone **1a** with the aldehyde **2a** also under solvent-free conditions in the ball mill. The reactions were conducted in the vibrational ball mill in three 90 min cycles (4.5 h in total, after shorter milling times conversion was not complete). The yield of product **3a** strongly depended on a molar ratio of enone **1a** to aldehyde **2a**. The reaction with five equivalents of enone **1a** gave after 4.5 h 74% of the product **3a**, while the reaction with only three equivalents of ketone **1a** gave under the same conditions 42% of the product **3a**. The reaction with equimolar amounts of reactants gave only 27% of pyranone **3a** (Table 1, entry 10). In ball-milling experiments, liquid acetic acid was replaced by solid benzoic acid because milling is more efficient with solid material. The reaction without benzoic acid proceeded slowly, and only 10% yield of the product was obtained. The yield of pyranone **3a** (74%) obtained under solvent-free conditions in ball mill after 4.5 h was better than yields achieved under classical condition for several days and comparable to result obtained in CH_2Cl_2 under ultrasonic irradiation for 5.5 h. Chiral catalysts (**C2**, **C7**, thiourea derivatives, chiral imidazolidinones) were inactive in solvent-free reactions in ball mill.

When acidic ionic liquid ([bmim][HSO_4]) was used as a solvent, reaction did not proceed and only unreacted starting materials were isolated.

Next, we tried to adapt the oxa-Diels-Alder reaction to a continuous flow microreactor (Fig. 3). Flow microreactors have been widely used for reactions with immobilized catalysts,[32] but just a few homogeneous catalytic reactions have been investigated under these conditions.[33] Instrument set-up presented on Fig. 3 was used for the reaction of enone **1a** with aldehyde **2a** with pyrrolidine (**C1**) catalysis in toluene at 50 °C, which were the best conditions under MWI (Table 1, entry 9). The product **3a** was isolated in 64% yield (Table 1, entry 11). A large number of unidentified side products were observed, when the reaction proceeded in the flow microreactor at higher temperatures (60–80 °C). Optimum reaction time was 2h, as shorter times, for instance, 50 min residence time led to only 53% yield of the product. If the reaction was performed without *pre-stirring* of the compound **1a** with pyrrolidine and acetic acid, that is without T mixer, the yield was lower, only 51%. Chiral catalysts **C3**, **C5** and (*S*)-bis(3,5-bis(trifluoromethyl)phenyl) (pyrrolidin-2-yl)methanol were in flow reactor inactive.

Table 1 Oxa-Diels-Alder reactions of **1a** with **2a** under various conditions.

Entry	Solvent	Additive	Condition	Yield of **3a** (%)
1	CH_2Cl_2	AcOH	48 h, r.t., stirring	65
2	CH_2Cl_2	AcOH	2 h, 50 °C, stirring	45
3	CH_2Cl_2	AcOH	5.5 h, ultrasonic bath	69
4	Water	AcOH	72 h, r.t., stirring	29 (22)[a]
5	Water	$PhCO_2H$	8 h, ultrasonic bath	50 (15)[a]
6	Toluene	AcOH	72 h, r.t., stirring	46
7	CH_2Cl_2	AcOH	2 h, 50 °C, MWI	45
8	Toluene	AcOH	2 h, 40 °C, MWI	60 (94)[b]
9	Toluene	AcOH	50 min, 50 °C, MWI	65 (97)[b]
10	-	$PhCO_2H$	4.5 h, ball mill	74[c] (42[d], 27[e])
11	Toluene	AcOH	2 h, 50 °C, flow microreactor	64

[a] Yield of the aldol product **4**. [b] In parentheses aldehyde conversion determined by NMR. [c] Molar ratio **1a**:**2a** was 5:1. [d] Molar ratio **1a**:**2a** was 3:1. [e] Molar ratio **1a**:**2a** was 1:1.

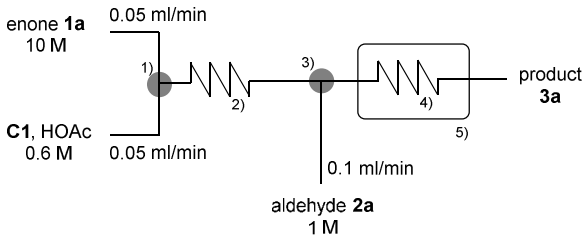


Fig. 3 Diagram representing flow reactor set-up: 1) T-mixer (teflon); 2) residence time unit 3 mL (teflon tubing); 3) LTF MS mixer (glass); 4) residence time unit 24 mL (teflon tubing); 5) heating bath.

Then, we studied a synthetic utility of this method. Based on the above mentioned evaluation of different activation techniques, we focused more on ultrasound and ball-milling. The reaction of (*E*)-pent-3-en-2-one (**1b**) with 4-nitrobenzaldehyde (**2a**) with pyrrolidine (**C1**) as a catalyst in CH_2Cl_2 afforded the corresponding pyranone **3b** in 77% yield. When we used equimolar amounts of **C1** and thiourea **C9** (15 mol%), the product **3b** was isolated in only 49% yield in racemic form (Table 2, entries 1 and 2). The product **3b** was obtained in similar yield (53%), when the reaction was performed under microwave irradiation at 50 °C for 2 h. Somewhat better yield (76%) of pyranone **3b** was achieved under solvent-free conditions in the ball mill after 4.5 h. Solid benzoic acid was used instead of acetic acid as acidic additive (Table 2, entries 3 and 4). The oxa-Diels-Alder reaction of ketone **1b** with 4-formylbenzonitrile (**2b**) afforded pyranone **3c** in 56% yield (Table 2, entry 5). Again, the yield of the product **3c** decreased (42%), when the reaction proceeded under microwave irradiation (at 50 °C for 2 h). The best yield of the product **3c** (68%) was obtained in ball mill without solvent with benzoic acid (Table 2, entries 6 and 7). Solvent-free conditions in ball mill were successfully applied also in the preparation of

products **3d** (51%), **3e** (75%) and **3f** (64%) (Table 2, entries 8–10).

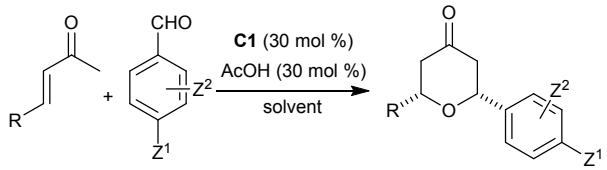
Oxa-Diels-Alder reactions of ketone **1a** with 4-(trifluoromethyl)benzaldehyde (**2e**), 4-chlorobenzaldehyde (**2f**) and 4-fluorobenzaldehyde (**2g**) in CH_2Cl_2 at room temperature for 48 h did not proceed and only starting materials were isolated after these reactions. Similarly, 4-fluorobenzaldehyde (**2g**) was inactive in the reaction with ketone **1b** (Table 2, entries 11–14).

The reactions of (*E*)-4-methoxybut-3-en-2-one (**1c**) with aldehyde **2a** in CH_2Cl_2 under pyrrolidine catalysis provided only (*E*)-4-(pyrrolidin-1-yl)but-3-en-2-one (**1e**), the product of substitution of methoxy group with pyrrolidine. We also tried α,β-unsaturated ketone **1e** in the oxa-Diels-Alder reaction with aldehyde **2a**, but the reaction did not proceed in CH_2Cl_2 at room temperature, nor under microwave irradiation. Only starting materials were isolated after reaction in the ball mill too. No reaction was observed with (*E*)-4-(benzylamino)but-3-en-2-one (**1d**) and 4-nitrobenzaldehyde (**2a**) in CH_2Cl_2 at room temperature, nor in water under ultrasonic irradiation.

We have tested also nitrosobenzene as a dienophile, but no product of hetero-Diels-Alder reaction was observed. Only starting materials were detected in the reaction mixture after the reactions in CH_2Cl_2 at room temperature with (*S*)-proline or pyrrolidine as a catalyst.

In terms of overall efficiency (cleanness of reaction, yield of the desired product, practicality, reaction time), ball milling seems to be the most useful method for oxa-Diels-Alder reaction of enone **1b** with several aldehydes **2**. Ultrasound and microwaves were also effective both with solvent and as neat. However, solvent free experiments in connection with ultrasound and microwave were limited to liquid reagents. Another practical limitation connected with typical microwave reactor is minimum volume, to which reaction vessel needs to be filed, in our case 2 mL.

Table 2 Oxa-Diels-Alder reactions of enones **1a-e** with aldehydes **2a-g**



1a, R = Ph
1b, R = Me
1c, R = OMe
1d, R = NHBn
1e, R = 

2a. Z^1 = NO_2, Z^2 = H
2b, Z^1 = CN, Z^2 = H
2c, Z^1 = H, Z^2 = 3-NO_2
2d, Z^1 = NO_2, Z^2 = 2-NO_2
2e, Z^1 = CF_3, Z^2 = H
2f, Z^1 = Cl, Z^2 = H
2g, Z^1 = F, Z^2 = H

3a, R = Ph, Z^1 = NO_2, Z^2 = H
3b, R = Me, Z^1 = NO_2, Z^2 = H
3c, R = Me, Z^1 = CN, Z^2 = H
3d, R = Ph, Z^1 = H, Z^2 = 3-NO_2
3e, R = Me, Z^1 = H, Z^2 = 3-NO_2
3f, R = Ph, Z^1 = NO_2, Z^2 = 2-NO_2

Entry	1	2	Conditions	Yield of **3** (%)
1	**1b**	**2a**	48 h, r.t., CH_2Cl_2, stirring	77 (**3b**)
2[a]	**1b**	**2a**	48 h, r.t., CH_2Cl_2, stirring	49 (**3b**)
3	**1b**	**2a**	2 h, 50 °C, CH_2Cl_2,MWI	53 (**3b**)
	1b	**2a**	2 h, 60%, neat, MWI	60 (**3b**)
	1b	**2a**	5.5 h, neat, ultrasonic bath	67 (**3b**)
	1b	**2a**	5.5 h, CH_2Cl_2, ultrasonic bath	63 (**3b**)
4	**1b**	**2a**	4.5 h, ball mill, $PhCO_2H$	76 (**3b**)
	1b	**2a**	48 h, solvent-free, dry stirring	67 (**3b**)
5	**1b**	**2b**	48 h, r.t., CH_2Cl_2, stirring	56 (**3c**)
6	**1b**	**2b**	2 h, 50 °C, CH_2Cl_2, MWI	42 (**3c**)
7	**1b**	**2b**	4.5 h, ball mill, $PhCO_2H$	68 (**3c**)
8	**1a**	**2c**	4.5 h, ball mill, $PhCO_2H$	51 (**3d**)
9	**1b**	**2c**	4.5 h, ball mill, $PhCO_2H$	75 (**3e**)
10	**1a**	**2d**	4.5 h, ball mill, $PhCO_2H$	64 (**3f**)
11	**1a**	**2e**	48 h, r.t., CH_2Cl_2, stirring	0
12	**1a**	**2f**	48 h, r.t., CH_2Cl_2, stirring	0
13	**1a**	**2g**	48 h, r.t., CH_2Cl_2, stirring	0
14	**1b**	**2g**	48 h, r.t., CH_2Cl_2, stirring	0
15	**1d**	**2a**	72 h, r.t., CH_2Cl_2, stirring	0
16	**1d**	**2a**	8 h, H_2O, ultrasonic bath	0
17	**1e**	**2a**	72 h, r.t., CH_2Cl_2, stirring	0
18	**1e**	**2a**	2 h, 50 °C, CH_2Cl_2, MWI	0
19	**1e**	**2a**	4.5 h, ball mill, $PhCO_2H$	0

[a] Equimolar amounts (15 mol%) of **C1** and **C9** were used.

In an attempt to establish enantioselective oxa-Diels-Alder reaction of enones **1** with aldehydes, we have investigated a range of chiral organocatalysts (Fig. 1 and 2). As a benchmark, we selected the oxa-Diels-Alder reaction of enone **1a** with aldehyde **2a**. Previous screening confirmed that CH_2Cl_2 at room temperature and acetic acid (30 mol%) as an acidic additive were appropriate reactions conditions for testing of chiral organocatalysts. As the first selection principle, we have chosen catalysts, which were likely to participate in an enamine activation of the α,β-unsaturated ketone **1a**. A variety of pyrrolidine derivatives **C1**–**C7** was screened. Chiral donors of hydrogen bonds can activate both ketones and aldehydes. Therefore, we have also tested several structurally diverse thioureas **C8**–**C14** and a squaramide catalyst **C15**.

(*S*)-Proline (**C2**) as well as silyl protected difenylprolinol **C7** were ineffective in this reaction. The product **3a** was isolated in only 19 or 16% yield after 48 h with **C2** and **C7**, respectively (Table 3, entries 1 and 7). Prolonging the reaction time had no effect on the yield of the product **3a**. Using (*S*)-

prolinol (**C3**), the reaction yielded in 46% of the product **3a** with e.r. 63:37. Interestingly, the reaction with an equimolar mixture of catalyst **C3** and pyrrolidine (**C1**) gave somewhat better yield (52%) after 48 h, but e.r. remained practically the same (62:38) (Table 3, entries 2 and 3). When we performed addition of **1a** with **2a** using catalyst **C3** at 5 °C for three days the yield of **3a** dropped to 27%.

Similar results were also obtained with catalyst **C4** with a primary amino group. The product **3a** was isolated in 48% yield with similar e.r (61:39) (Table 3, entry 4). When catalysts **C5** and **C8** were used in the reaction of enone **1a** with aldehyde **2a**, the product **3a** was obtained in low yields (26 and 28%, respectively). Furthermore, these catalysts afforded the product **3a** in virtually racemic form (Table 3, entries 5 and 8). The highest yield of the product **3a** (82%) was obtained with catalyst **C6**, but enantioselectivity of the reaction was low (e.r. 53:47) (Table 3, entry 6). The reactivity of chiral catalyst **C6** is even slightly higher than that of pyrrolidine (**C1**). Hydrogen-bonding catalysts itself were not effective, as documented by experiments with catalysts **C8** and **C15** (Table 3, entries 8 and 11). We hypothesised that a thiourea or squaramide catalyst would activate the aldehyde, and pyrrolidine would activate the ketone, thus leading to dual activation of both reaction partners. Therefore, we tried the reaction with an equimolar mixture (15 mol%) of catalysts **C9** and **C1** gave within 72 h 80% of pyranone **3a**. Unfortunately, the product **3a** was isolated in almost racemic form. Surprisingly, when we increased catalysts loading to 30 mol%, the product **3a** was isolated in only 49% yield after 48 h (Table 3, entries 9 and 10).

Next, we performed a series of experiments with 50 mol% of pyrrolidine (**C1**) with the addition of a small amount (5 mol%) of chiral thioureas **C10**–**C14**. We assumed that pyrrolidine would generate a dienamine with enone **1a** and chiral thioureas would activate aldehyde **2a** through hydrogen bonds with a nitro group and thus render cycloaddition enantioselective. Reactions with pyrrolidine (**C1**) (50 mol%) and thioureas **C10**–**C14** (5 mol%) in CH_2Cl_2 using acetic acid (30 mol%) as an acid additive gave pyranone **3a** in good yields (45–70%). In all cased, however, the product **3a** was isolated as a racemic mixture (Table 3, entries 12–16).

Table 3. Oxa-Diels-Alder reactions of **1a** with **2a** with chiral organocatalysts

Entry	Catalyst	Time (h)	Yield of **3a** (%)	e.r. of **3a**
1	**C2** (30 mol%)	48	19	n.d.
2	**C3** (30 mol%)	68	46	63:37
3	**C3** (15 mol%) + **C1** (15mol%)	48	52	62:38
4	**C4** (30 mol%)	48	48	61:39
5	**C5** (30 mol%)	48	26	59:41
6	**C6** (30 mol%)	48	82	53:47
7	**C7** (30 mol%)	48	16	n.d.
8	**C8** (30 mol%)	48	28	58:42
9	**C9** (15 mol%) + **C1** (15 mol%)	72	80	57:43
10	**C9** (30 mol%) + **C1** (30 mol%)	48	49	50:50
11	**C15** (30 mol%)	72	traces	n.d.
12	**C1** (50 mol%) + **C10** (5 mol%)	48	45	50:50
13	**C1** (50 mol%) + **11** (5 mol%)	48	70	50:50
14	**C1** (50 mol%) + **C12** (5 mol%)	48	45	50:50
15	**C1** (50 mol%) + **C13** (5 mol%)	48	61	50:50
16	**C1** (50 mol%) + **C14** (5 mol%)	48	63	50:50

Experimental conditions: **1a** (4.0 mmol), **2a** (1.0 mmol), AcOH (0.30 mmol), catalyst **C1**-**C7**, CH_2Cl_2 (3 mL), r.t.

Conclusions

Oxa-Diels-Alder reaction of acyclic α,β-unsaturated ketones with aldehydes were studied under classical conditions, under ultrasonic and microwave irradiation, under solvent-free conditions in ball mill and flow microreactor. Non-classical conditions improved reaction course, yield as well as reaction rate. The largest positive influence had microwave irradiation and ball milling. The reaction worked well under solvent-free conditions also using ultrasound and microwave irradiation. The most efficient method overall is ball milling, which considerably shortens reaction times and is applicable as long as at least one of the reaction components was solid. Enantioselectivities up to e.r. 63:37 were observed with chiral pyrrolidine-based organocatalysts.

Experimental section

General

NMR spectra were recorded on Varian NMR SystemTM 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C). Chemical shifts (δ) are given in ppm relative to tetramethylsilane. Flash chromatography was performed on silica gel 60A, 0.035–0.070 nm, from Fluka. Thin-layer chromatography was performed on Merck TLC-plates silica gel 60, F-254. Enantiomer purity was determined by HPLC on Chiralcel AD-H (Daicel Chemical Industries) column using hexane/*i*PrOH as a mobile phase and UV detection. Microwave reactions were performed in Microwave Synthesis Reactor Monowave 300 (Anton Paar, IR sensor for temperature control, sealed vessel), sonochemical reaction proceeded in ultrasonic cleaning bath Kraintek 6 (20 kHz) in a glass flask closed with rubber septum under Ar atmosphere. Vibrational ball mill MM400 (Retsch, 20 Hz) was used for solvent-free reactions. Flow system was custom made but assembled from commercially available parts. Detailed description, including pictures, is in supporting information. IR spectra were recorded on Thermo Scientific

Nicolet iS10 spectrometer. HRMS were measured on a Thermo Velos Pro Orbitrap instrument by electrospray ionisation (ESI). All the melting points were determined on Kofler apparatus *Electrothermal IA-9200*.

Synthetic procedure for reactions in solvents

α,β-Unsaturated ketone (4.0 mmol), catalyst (0.30 mmol) and acid (0.30 mmol) were dissolved in solvent (3 mL) and the reaction mixture was stirred for 30 min at room temperature. An aldehyde (1.0 mmol) was added and the reaction mixture was then stirred at room temperature, or irradiated in ultrasonic bath at 20 kHz, or irradiated in a microwave reactor for the time given in Tables 1–3. Solvent was evaporated and product was purified by flash chromatography (SiO_2, hexane/EtOAc 4:1).

Synthetic procedure for reactions in ball mill

The ball mill reactor (stainless steel, internal volume 1.5 mL) was filled with (*E*)-4-phenylbut-3-en-2-one (**1a**) (730 mg, 5.0 mmol), 4-nitrobenzaldehyde (**2a**) (151 mg, 1.0 mmol), pyrrolidine (**C1**) (21 mg, 0.30 mmol) and benzoic acid (36.6 mg, 0.30 mmol) and grinded for 3×90 min (1 steel ball Ø 5 mm or 2 balls with Ø 3 mm). Reaction mixture was then washed out from the reactor with CH_2Cl_2 (10 mL). Solvent was evaporated and product **3a** was purified by flash chromatography (SiO_2, hexane/EtOAc 4:1).

Synthetic procedure for reactions in flow reactor

The reaction was conducted in a reactor consisting of a 3 mL mixing unit and a 24 mL heated (50 resp. 60 °C) retention unit and three inlets (Fig. 1). Reagents were introduced using a syringe pump. A solution of (*E*)-4-phenylbut-3-en-2-one (**1a**) (65 mmol) in the solvent was introduced at one inlet at a flow rate of 0.05 mL/min while a solution of pyrrolidine (**C1**) (3.9 mmol) and acetic acid (3.9 mmol) in the same solvent was introduced from the other inlet at the same flow rate. Total output was 0.1 mL/min. After mixing these reagents, 4-nitrobenzaldehyde (**2a**) (13 mmol) was introduced from the third inlet in the same solvent at a flow rate of 0.1 mL/min. Total output was 0.2 mL/min (2 h of residence time). The collected solution was concentrated under reduced pressure. Residues were purified by flash chromatography (heptane/ethylacetate 5:1) to afford the title compound.

(2*R*,6*S*)-2-(4-nitrophenyl)-6-phenyldihydro-2*H*-pyran-4(3*H*)-one (3a)

The compound was prepared according to procedure described above. The pure product was obtained as yellow crystals (220 mg, 74 %). Data: mp 95 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.26 (d, J = 8.8 Hz, 2H, $PhNO_2$), 7.64 (d, J = 8.8 Hz, 1H, $PhNO_2$), 7.51–7.33 (m, 5H, Ph), 4.97 (dd, J_1 = 11.7, J_2 = 2.6 Hz, 1H, $CHPhNO_2$), 4.88 (dd, J_1 = 10.2, J_2 = 4.2 Hz, 1H,CHPh), 2.89–2,60 (m, 4H, CH_2COCH_2). ^{13}C NMR (75 MHz, $CDCl_3$, δ) 204.7, 147.6, 147.6, 140.1, 128.8, 128.4, 126.4, 125.6, 124.0, 79.2, 77.8, 49.5, 49.3. ^{1}H and ^{1}3C NMR spectroscopic data are in agreement with those reported in literature.[25]

(2*R*,6*R*)-2-methyl-6-(4-nitrophenyl)dihydro-2*H*-pyran-4(3*H*)-one (3b)

The compound was prepared according to procedure described above. The pure product was obtained as yellow crystals (179 mg, 76 %). Data: mp 122 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.24 (d, J = 8.9 Hz, 2H), 7.60–7.53 (m, 2H), 4.77 (dd, J_1 = 11.7, J_2 = 2.7 Hz, 1H), 3.96 (ddd, J_1 = 11.2, J_2 = 6.1, J_3 = 2.8 Hz, 1H), 2.66 (ddd, J_1 = 14.4, J_2 = 2.8, J_3 = 2.0 Hz, 1H), 2.56–2.33 (m, 3H), 1.45 (d, J = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ) 205.3, 147.9, 147.5, 126.3, 123.8, 77.4, 73.8, 49.1, 48.9, 22.1. IR ν = 3081.59, 2974.34, 2891.11, 1712.11, 1517.98, 1361.03, 1342.85, 1294.51, 1062.51 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{13}NO_4$ – $[M]^-$ 235.0845, found 235.0852.

4-((2*R*,6*R*)-6-methyl-4-oxotetrahydro-2*H*-pyran-2-yl)benzonitrile (3c)

The compound was prepared according to procedure described above. The pure product was obtained as yellow crystals (146 mg, 68 %). Data: mp 99 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.73–7.62 (m, 2H), 7.55–7.44 (m, 2H), 4.72 (dd, J_1 = 11.7, J_2 = 2.8 Hz, 1H), 3.94 (ddd, J_1 = 11.2, J_2 = 6.1, J_3 = 2.8 Hz, 1H), 2.69–2.29 (m, 4H), 1.43 (d, J = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ) 205.4, 145.9, 132.5, 126.2, 118.6, 111.8, 77.6, 73.7, 49.1, 48. 6, 22.1. IR ν = 2978.97, 2862.39, 2227.62, 1714.04, 1351.02, 1309.04, 1257.01, 1164.00, 1140.48, 1062.19, 825.84 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{13}NO_2$ – $[M+H]^+$ 216.1019, found 216.1018.

(2*R*,6*S*)-2-(3-nitrophenyl)-6-phenyldihydro-2*H*-pyran-4(3*H*)-one (3d)

The compound was prepared according to procedure described above. The pure product was obtained as yellow oil (150 mg, 51 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.18 (dd, J = 8.2, 1.3 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.48 – 7.39 (m, 4H), 7.35 (t, J = 7.3 Hz, 1H), 4.96 (dd, J = 11.8, 2.6 Hz, 1H), 4.88 (dd, J = 10.3, 4.1 Hz, 1H), 2.81 – 2.65 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 204.6, 148.5, 142.7, 140.1, 131.7, 129.7, 128.8, 128.4, 125.6, 123.1, 120.8, 79.2, 77.7, 49.5, 49.2. IR ν = 3087.49, 3066.13, 2966.95, 2867.44, 1717.34, 1526.15, 1344.46, 1309.38, 1243.79, 1144.71, 1054.09, 735.42, 696.22 cm^{-1}. HRMS (ESI): calcd for $C_{17}H_{15}NO_4$ – $[M+Na^+]$ 320.0893, found 320.0892.

(2*R*,6*R*)-2-methyl-6-(3-nitrophenyl)dihydro-2*H*-pyran-4(3*H*)-one (3e)

The compound was prepared according to procedure described above. The pure product was obtained as yellow crystals (176 mg, 75 %). Data: mp 151 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.18 (dd, J = 8.2, 1.3 Hz, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 4.77 (dd, J = 11.8, 2.7 Hz, 1H), 3.97 (ddd, J = 11.5, 6.1, 2.6 Hz, 1H), 2.69 – 2.65 (m, 1H), 2.55 – 2.47 (m, 2H), 2.40 (dd, J = 14.1, 11.1 Hz, 1H), 1.45 (d, J = 6.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 205.4, 148.5, 142.9, 131.6, 129.6, 122.9, 120.8, 77.3, 73.8, 49.1, 48.9, 22.1. IR ν = 3121.10, 2973.32, 2933.70, 2881.22, 1709.40, 1522.71, 1343.31, 1272.18, 1257.92, 1057.03, 810.09, 683.69 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{13}NO_4$ – $[M+Na^+]$ 258.0737, found 258.0737.

(2*R*,6*S*)-2-(2,4-dinitrophenyl)-6-phenyldihydro-2*H*-pyran-4(3*H*)-one (3f)

The compound was prepared according to procedure described above. The pure product was obtained as yellow crystals (220 mg, 64 %). Data: mp 113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.3 Hz, 1H), 8.54 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.25 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 4.5 Hz, 5H), 5.56 (dd, *J* = 11.5, 2.6 Hz, 1H), 4.92 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.06 (ddd, *J* = 14.6, 2.5, 1.6 Hz, 1H), 2.80 (dd, *J* = 9.2, 6.1 Hz, 2H), 2.57 (dd, *J* = 14.4, 11.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.2, 147.3, 147.2, 142.4, 139.6, 129.8, 128.8, 128.6, 127.9, 125.63, 120.2, 79.0, 74.3, 48.8, 47.7. IR ν = 3084.69, 3062.42, 3026.64, 1715.92, 1608.25, 1527.73, 1340.46, 1307.71, 1238.99, 1060.99, 696.81 cm^{-1}. MS (ESI/APCI): calcd for $C_{17}H_{14}N_2O_6$ – $[M\text{-}H^+]$ 341.1, found 341.1. Elem. anal. calcd for $C_{17}H_{14}N_2O_6$ C 59.65, H 4.12, N 8.18; found C 59.82, H 4.13, N 8.04.

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Electronic Supplementary Information (ESI) available: pictures of ^{1}H and ^{13}C NMR spectra and HPLC chromatograms. See DOI: 10.1039/b000000x/

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