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Tandem catalysis for the synthesis of 2-alkylidene cyclohexenones

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ABSTRACT

(5*R*,6*S*,*E*)-5-Alkyl-2-(2-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enones, have been obtained by a domino reaction using tandem catalysis with a Nazarov reagent **3**, and several unsaturated aldehydes.

1. Introduction

Organocatalysis is an area of organic chemistry in constant evolution.[1] One of the fields of research in this area that has inspired most interest to organic chemists is the development of tandem reactions due to their ability to provide complex compounds in a very simple manner, lowering the cost of the synthesis.[1c,2]

Of special interest to us is the excellent work of Prof. Ramachary et al. on the synthesis of functionalised push–pull olefins and phenols with Hagemmann's ester, using multicatalysis reactions.[3] Related works include the synthesis of cyclohexanones by a tandem Michael/Morita–Baylis–Hillman reaction using Nazarov reagents and prolinol derivatives as organocatalysts,[4] and the Michael–Knoevenagel condensation reaction using Nazarov reagents.[5]

The sulfone group is one of the latest groups to be incorporated into the panoply of organic functionalities used in organocatalysis[6] and has attracted very soon the attention of many researchers due to its versatility. In our group we were interested by the methodology of Prof. Jørgensen to obtain 2-alkylidene cyclohexanones[4,5] and that of Profs. Garcia Ruano and Alemán to obtain chiral cyclohexenones.[7]

2. Results and discussion

Previous work by Prof. Jørgensen described that the tandem reaction between compound **A**, Fig. 1, and the Nazarov reagent **B**,

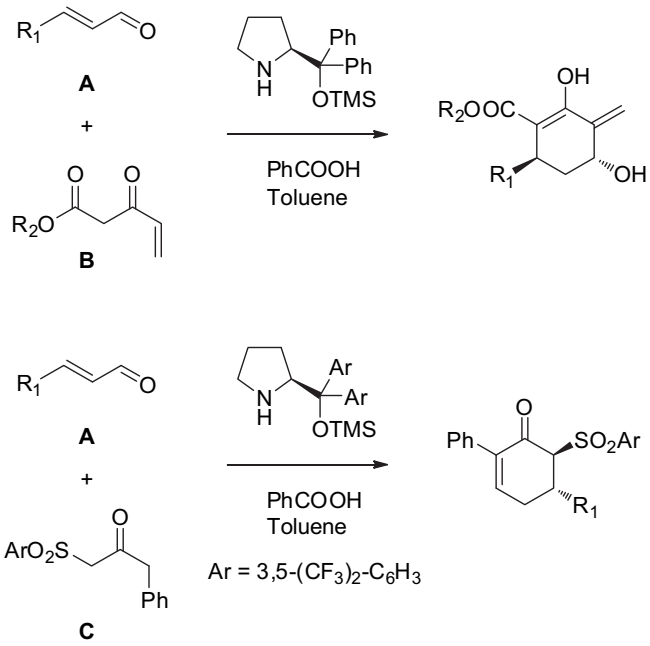

Fig. 1. Use of Nazarov reagents for the synthesis of cyclohexenones.

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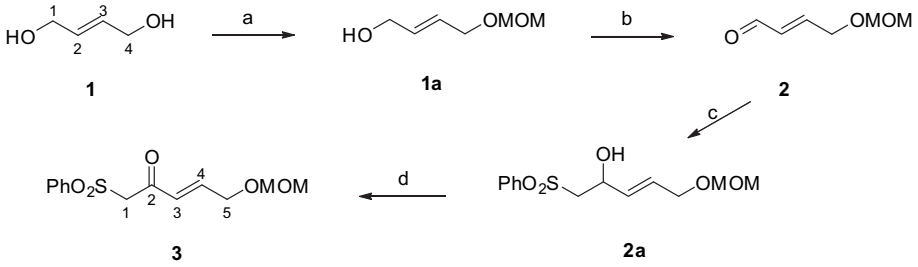
when substituted with a methyl group at the γ or δ positions of the alkene did not take place, and only a sluggish Michael addition is observed due to the steric hindrance associated with the Morita–Baylis–Hillman reaction.[4b] The groups of Profs. Garcia Ruano and Alemán, established an easy procedure for the synthesis of chiral cyclohexenones starting from α,β-unsaturated aldehydes, **A**, and α,β-keto sulfones, such as **C**[7a] Fig. 1.

2.1. Synthesis of Nazarov reagent 3

Our group has been interested in the reactivity of the sulfone group, and its application in organocatalysis,[8] so we initiated our research by preparing Nazarov reagent **3**, to obtain 2-alkylidene cyclohexenones via tandem catalysed reactions.

Compound **3** was easily synthesised in high yield from the commercially available diol **1** in four steps Scheme 1.



Scheme 1. Reagents and conditions for the synthesis of the Nazarov reagent **3**: (a) MOMCl, NaH, THF, 0 °C, 87%; (b) PDC (2 equiv), molecular sieves, DCM, rt, 72%; (c) Methylphenylsulfone (0.9 equiv), *n*-BuLi (0.9 equiv), THF, −78 °C, 63%; PDC (2 equiv), molecular sieves, rt, 50%.

(*E*)-1,4-Butanediol was protected under standard conditions to obtain the MOM protected derivative **1a**,[9] this was oxidised with PDC in DCM to give aldehyde **2**[10] in good yield over two steps. Addition of the lithium derivative of methylphenylsulfone to aldehyde **2** gave alcohol **2a**, this was oxidised to the corresponding ketone **3** as before, and allowed us to proceed with the organocatalysis study.

2.2. Reaction of 3 with different catalysts and conditions

We started our study with the reaction of compound **3** with (*E*)-2-pentenal **4**, following conditions proposed by Profs. Garcia Ruano and Alemán[7] with different organocatalysts and additives, already used in similar reactions,[7] for: table 1.

As shown in Table 1, the reaction does not take place without catalyst, entry 1, or even with additive, entry 2. When pyrrolidine is used as the catalyst, only decomposition is observed, entry 3. The use of *i*-PrOH as solvent accelerates the reaction when LiOAc is used as the additive, entries 4–6, in all cases giving the cyclisation product **7** in a diastereomeric ratio 2/1 of the olefins and no enantioselectivity. The anti relative stereochemistry for the sulfone and the ethyl group was established by NOE spectroscopy, as no NOE coupling was observed between H5 and H6, in both compounds. In the case of the olefin by the NOEs observed for both compounds, as shown in Fig. 2.

The use of benzoic acid as the additive stops the cyclisation and gives a mixture of diastereomeric aldehydes **6a** (*syn*) and **6b** (*anti*) in a 1/1 ratio in a good yield, but we were unable to establish the enantiomeric ratio, entry 7. In entries 8 and 9, without additive, the yield decreases slightly and the reaction is slower, but the same cyclisation products are obtained in the same diastereomeric ratio, with no enantioselectivity. Similar results have been obtained previously in similar processes.[11] Racemic proline was used to establish the conditions for the enantiomeric ratio determination by HPLC, giving the cyclisation product as the same mixture of diastereomeric olefins, entry 10. Catalysts **5a** and **5b**[12] gave good results in the Michael addition affording the mixture of diastereoisomeric aldehydes **6** *syn*/*anti* (1/1) at the carbon flanked by the carbonyl and sulfonyl group, but they did not give any cyclisation product, entries 11–15. MacMillan catalysts[13] **5c** gave no reaction, entries 16 and 17 and **5d** gave similar result as the catalyst **5b**, but in longer time.

2.3. Reaction of 3 with different unsaturated aldehydes using proline as catalyst

Although proline gave no enantioselectivity, the synthesis of the 2-alkylidene cyclohexenones **7** in a domino process in an easy and convenient manner is very significant. For this reason, and in order to check this reaction and extend its versatility, a variety of aldehydes **8**–**10** and **2** were chosen as starting materials.[14]

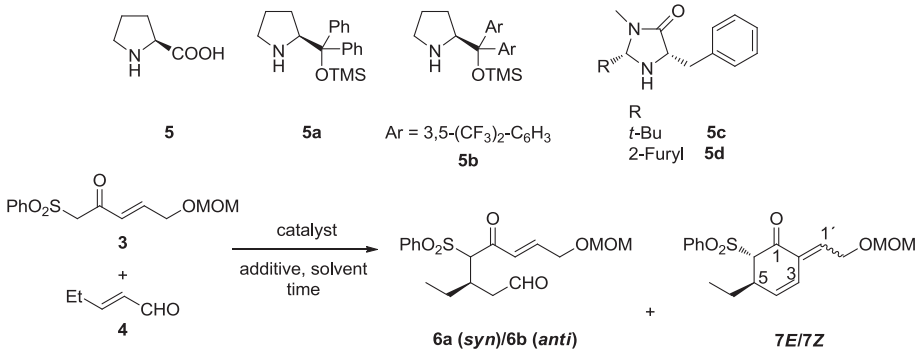
The results observed in Table 2, indicated that this domino reaction could be extended to several aldehydes, to provide different 2-alkylidene cyclohexenones. The reaction affords a 2/1 diastereomeric mixture of olefins in favour of the *E*-compound with no enantioselectivity. It is remarkable that bulkier alkyl chains led to better yields. In no case did this reaction proceed to the phenol structure under the reaction conditions. In order to obtain our goal, i.e., the synthesis of chiral 2-alkylidene cyclohexenones, we decided to carry out the domino reaction using two organocatalysts successively, in one pot.

2.4. Reaction of 3 with different unsaturated aldehydes using two catalysts in tandem

As Profs. Garcia Ruano and Alemán established, in a similar case, the reaction using catalyst **5b** proceed with high enantiomeric ratio to the Michael addition aldehydes.[7a] In order to obtain a better enantiomeric ratio, and increase the yield we chose to perform a tandem reaction, first obtaining the aldehydes **6** with enantiomeric excesses, using catalyst **5b**, and then adding proline to afford the cyclisation product. Although there is little difference between chloroform and isopropyl alcohol as solvents, entries 1 and 2 Table 3, $CDCl_3$ was the option selected in order to monitor the reaction by ^1H NMR, attending to the disappearance of the sulfone and the starting aldehyde employed. The reaction under the same conditions gives identical results using $CHCl_3$ as the solvent. The use of **5b** instead of **5d** is due to the reaction speed and better yields observed, entries 13, 14 and 18, 19, Table 1. When the reaction is completed, proline **5**, is added as the second catalyst. The reaction conditions were established using pentenal, hexenal and heptenal as aldehydes and extended to other alkyl aldehydes as **2** and **10**.

As shown in Table 3, entry 1, if isopropyl alcohol is used as solvent without any additive the reaction takes place in very good

Table 1
Screening of the reaction between Nazarov reagent **3** and (*E*)-2-pentenal **4**, using different catalysts and conditions



Entry	Catalyst	Additive	Solvent	Time[a] (h)	Yield[b] (%)		er[c]	dr[d]
					6a/**6b**	**7***E*/**7***Z*		
1			*i*-PrOH	6	S.M.		—	—
2		LiOAc	*i*-PrOH	6	S.M.		—	—
3	Pyrrolidine	LiOAc	*i*-PrOH	3	Decomposition		—	—
4	**5**	LiOAc	*i*-PrOH	3		40	1/1	2/1
5	**5**	LiOAc	EtOH	69		11	1/1	2/1
6	**5**	LiOAc	$CDCl_3$	13		60	1/1	2/1
7	**5**	B.A.	$CDCl_3$	120	60		n.d.	1/1
8	**5**	—	$CDCl_3$	63		33	1/1	2/1
9	**5**	—	*i*-PrOH	22		32	1/1	2/1
10	(±)**5**	LiOAc	*i*-PrOH	9		38	1/1	2/1
11	**5a**	LiOAc	$CDCl_3$	120	40		n.d.	1/1
12	**5a**	B. A.	$CDCl_3$	120	30		n.d.	1/1
13	**5b**	LiOAc	$CDCl_3$	42	38		n.d.	1/1
14	**5b**	B.A.	$CDCl_3$	23	32		n.d.	1/1
15	**5b**	LiOAc	*i*-PrOH	5	23		n.d.	1/1
16	**5c**	LiOAc	$CDCl_3$	120	S.M.		—	—
17	**5c**	B.A.	$CDCl_3$	120	S.M.		—	—
18	**5d**	LiOAc	$CDCl_3$	120	35		n.d.	1/1
19	**5d**	B.A.	$CDCl_3$	120	30		n.d.	1/1

All the reactions were carried out at rt, at 0.18 M, with 1/1 ratio of sulfone and aldehyde, with 20 mol % of catalyst and 20 mol % of additive. S.M.=starting materials. B.A.=benzoic acid.

[a] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored either by TLC or by ^1H NMR spectroscopy when $CDCl_3$ is used as the solvent).

[b] Yield referring to the mixtures of compounds **6a** (*syn*) and **6b** (*anti*) and to the mixtures of compounds **7***E* and **7***Z*, respectively (both with identical stereochemistry at C5 and C6).

[c] Enantiomeric ratio referred to the compounds **7***E* and **7***Z*, provided to be the same. The enantiomeric ratio was measured by HPLC analysis, carried out on a CHIRALCEL™ OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm.

[d] Diastereomeric ratio referred to the *syn*/*anti* ratio in the case of compounds **6a**/**6b** or to the *E*/*Z* ratio in the case of **7***E*/**7***Z*.

yield with good enantiomeric ratio. However using $CDCl_3$ as the solvent without an additive, although slightly lower yielding, leads to an excellent enantiomeric ratio. Optimal conditions to obtain the 2-alkylidene cyclohexenones were found to be $CDCl_3$, no additives, **5b** as the first catalyst, allowing to react until all starting materials have been consumed, followed by the addition of proline. This enables us to obtain the desired 2-alkylidene cyclohexenones in good yield and with good enantiomeric ratio.

The absolute configuration of the products is established tentatively according to the results obtained by Profs. Garcia Ruano and Alemán[7a] with similar sulfones and aldehydes and the Jørgensen group.[4b]

When bulkier alkyl aldehydes are employed, increased yields are obtained with excellent enantiomeric ratios. On the contrary, the use of aryl aldehydes does not produce any reaction. This

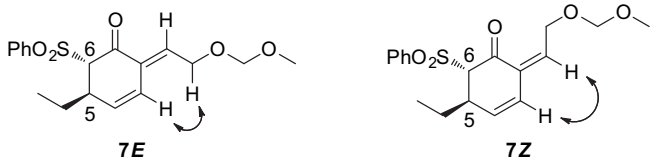
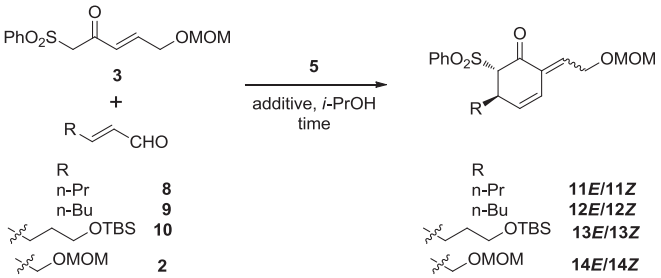


Fig. 2. NOEs that establish the configuration of the olefin for **7**.

Table 2
Proline as catalyst for the synthesis of 2-alkylidene cyclohexenones



Entry	Aldehyde	Additive	Time[a] (h)	Yield[b] (%)	Product	er[c]	dr[d]
1	**8**	LiOAc	8	69	**11**	1/1	2/1
2	**9**	LiOAc	8	80	**12**	1/1	2/1
3	**10**	LiOAc	6	51	**13**	1/1	2/1
4	**2**	LiOAc	16	31	**14**	1/1	2/1

All the reactions were carried out at rt, at 0.18 M, with 1/1 ratio of sulfone and aldehyde, with 20 mol % of **5**, and 20 mol % of additive. S.M.=starting materials.

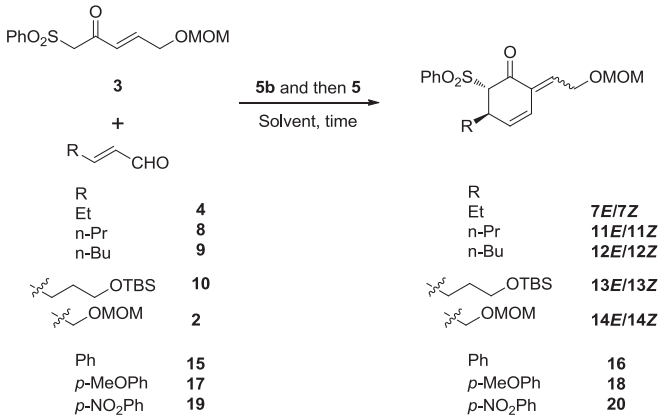
[a] Time in which highest yield was observed with no decomposition (the consumption of starting materials was monitored by TLC).

[b] Yield referring to the mixtures of isomers *E* and *Z*.

[c] Enantiomeric ratio referred to the compounds *E* and *Z*, provided to be the same. The enantiomeric ratio was measured by HPLC analysis, carried out on a CHIRALCEL™ OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm.

[d] *E*/*Z* diastereomeric ratio.

Table 3
Synthesis of 2-alkylidene cyclohexenones via tandem catalysis



Entry	Aldehyde	Solvent[a]	Time[b] (h)	Time proline[c] (h)	Yield[d] (%)	Product	er[e]	dr[f]
1	**4**	*i*-PrOH	10	96	77	**7***E*/**7***Z*	10/1	2/1
2	**4**	$CDCl_3$	10	48	73	**7***E*/**7***Z*	20/1	2/1
3	**8**	$CDCl_3$	26	48	75	**11***E*/**11***Z*	98/2	2/1
4	**9**	$CDCl_3$	26	48	50	**12***E*/**12***Z*	98/2	2/1
5	**10**	$CDCl_3$	30	115	46	**13***E*/**13***Z*	n.d.	2/1
6	**2**	$CDCl_3$	2	42	41	**14***E*/**14***Z*	95/5	2/1
7	**15**	$CDCl_3$	63	—	S.M.	**16***E*/**16***Z*	—	—
8	**15a**	$CDCl_3$	73	—	S.M.	**16a***E*/**16a***Z*	—	—
9[g]	**15b**	$CDCl_3$	73	—	Michael (50%)	**16b***E*/**16b***Z*	—	—

All the reactions were carried out at rt, at 0.18 M, with 1/1 ratio of sulfone and aldehyde, with 20 mol % of **5b** and 20 mol % of **5**.
S.M.=starting materials.
[a] Identical results are obtained when $CHCl_3$ is used as the solvent.
[b] Time in which intermediate aldehyde is formed (monitored either by TLC or by ^1H NMR spectroscopy when $CDCl_3$ is used as the solvent).
[c] Extra time after the addition of proline.
[d] Yield referring to the mixtures of isomers *E* and *Z*.
[e] Enantiomeric ratio referred to the compounds *E* and *Z*, provided to be the same. The enantiomeric ratio was measured by HPLC analysis, carried out on a CHIRALCEL™ OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm.
[f] *E*/*Z* diastereomeric ratio.
[g] This reaction does not proceed completely to the Michael addition product, being observed a 50% yield after 73 h; for this reason proline was not added.

behaviour has been reported by Profs. Garcia Ruano and Alemán[7a] in a similar case in which no reaction with cinnamaldehyde and other activated aldehydes was observed. In our case, oppositely only the Michael reaction with deactivated aryl aldehydes as **15b** is observed, although the addition step took more time.

The mechanism we postulate herein is a Michael reaction of the Nazarov reagent with the aldehyde through the standard catalytic cycle reported in the literature, A, Scheme 2.[4b,5] Once aldehydes **6** are formed, we understand that they enter in a new catalytic cycle B, in which a Morita–Baylis–Hillman reaction takes place with a concomitant Knoevenagel condensation[15] to obtain the cyclisation products.

3. Conclusions

Proline as the only organocatalyst is capable of producing 2-alkylidene cyclohexenones diastereoselectively, but with no enantiomeric excess, when using a Nazarov reagent as **3** and alkyl α,β-unsaturated aldehydes in a domino process. If two different catalysts are used successively, the domino reaction takes place in the same manner, but the 2-alkylidene cyclohexenones are produced with high enantioselectivity. The use of aryl aldehydes does not produce cyclisation products. All the compounds synthesised herein were stable and no transformation into phenols was detected.

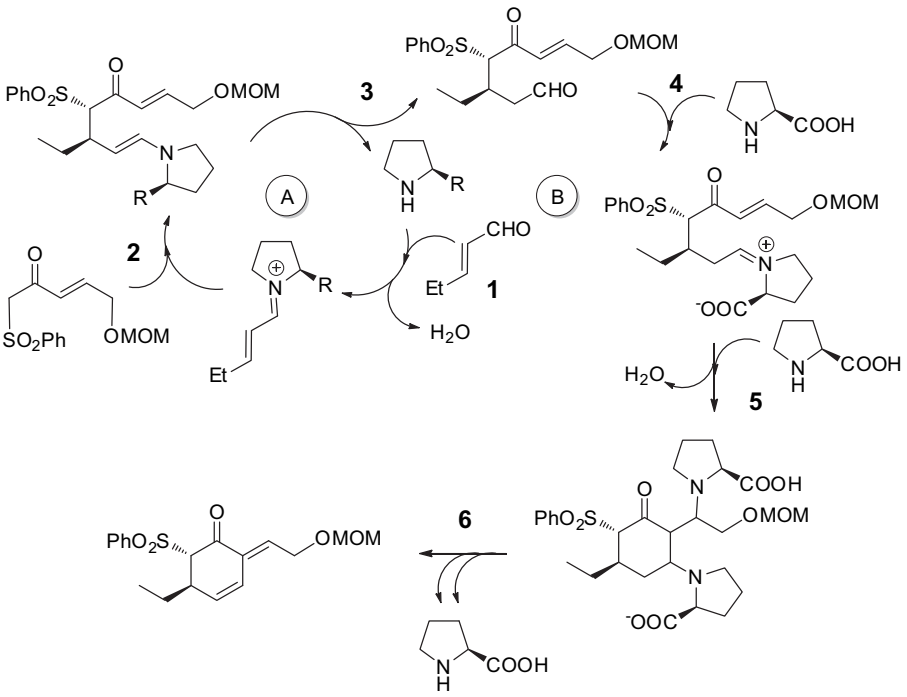
4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FT-IR or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ parts per million and coupling constants (J) are given in hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as m/z (% rel int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionisation (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cell. HPLC analyses were carried out on a CHIRALCEL™ OD-H column [cellulose tris(3,5-dimethylphenycarbamate)] on silica gel. Column chromatography was performed using silica gel 60 (230–400 mesh), with solvent systems indicated in the relevant experimental procedures. Dichloromethane was distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl under argon atmosphere prior to use. Hexane was distilled prior to use.

4.2. Synthesis of the Nazarov reagent, 3

*4.2.1. Monoprotection of diol **1** with MOMCl: (E)-4-methoxymethoxybut-2-en-1-ol, **1a**[9].* (*E*)-1,4-Butanediol (4 ml, 48.66 mmol) was dissolved in 480 ml of THF under Ar at 0 °C. NaH (60%, 1.95 g, 48.66 mmol) was added and left to stir for 10 min. Then MOMCl (3.70 ml, 48.66 mmol) was added and the mixture was stirred for 1 h. The reaction was quenched with H_2O, and extracted with



Scheme 2. Proposed mechanism for the Michael/Morita–Baylis–Hillman/Knoevenagel tandem reaction.

EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to give a crude transparent oil of monoprotected diol, **1a** (5.6 g, 87%). ν_{max} (liquid film) 3408, 2936, 2888, 1151, 1104, 1044, 920; δ_H (200 MHz; $CDCl_3$) 5.60 (2H, m, H2 and H3), 4.50 (2H, s, O–CH_2–O), 4.04 (4H, m, H1 and H4), 3.24 (3H, s, O–CH_3); δ_C (50 MHz; $CDCl_3$) 132.9, 127.5, 95.5, 62.7, 58.3, 55.4.

*4.2.2. Oxidation of **1a** with PDC: (E)-4-methoxymethoxybut-2-enal: **2**[10].* A mixture of monoprotected diol **1a** (2.32 g, 17.60 mmol) and molecular sieves was dissolved in 88 ml of DCM under Ar and stirred at rt for 5 min. PDC (13.2 g, 35.20 mmol) was added and left to stir for 4 h. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford a crude brown oil **2** (1.64 g, 72%). ν_{max} (liquid film) 2949, 2891, 1691, 1153, 1114, 1066, 1030, 968, 921; δ_H (200 MHz; $CDCl_3$) 9.48 (1H, d, J=7.9 Hz, CHO), 6.78 (1H, dt, J=15.7, 4.0 Hz, H3), 6.25 (1H, ddt, J=15.7, 7.9, 2.0 Hz, H2), 4.58 (2H, s, O–CH_2–O), 4.25 (2H, dd, J=4.0, 2.0 Hz, H4), 3.28 (3H, s, O–CH_3); δ_C (50 MHz; $CDCl_3$) 193.3, 153.0, 131.7, 96.3, 65.9, 55.6.

*4.2.3. Addition of methylphenylsulfone to **2**: (E)-5-(methoxymethoxy)-1-(phenylsulfonyl)pent-3-en-2-ol, **2a**.* Methylphenylsulfone (3.27 g, 20.9 mmol) was dissolved in 190 ml of THF under Ar at −78 °C. *n*-BuLi (1.6 M in hexanes, 13 ml, 20.9 mmol) was added and the mixture was stirred 10 min. Separately, **2** (3.02 g, 23.23 mmol) was dissolved in 42 ml of THF under Ar at rt. This solution was added via cannula to the former one and the mixture was stirred at −78 °C under Ar for 1 h. Then the reaction was quenched with a NH_4Cl saturated solution and extracted with EtOAc. The combined organics were washed with H_2O, dried (Na_2SO_4), filtered and concentrated in vacuo to leave a crude yellow oil. Flash chromatography (hexane/EtOAc, 7/3) afforded **2a** (3.75 g, 63%). ν_{max} (liquid film) 3457, 2932, 2884, 1305, 1145, 1086, 1041; δ_H (200 MHz; $CDCl_3$) 7.92 (2H, dd, J=8.2, 1.4 Hz, ArH_{ortho}), 7.73–7.48 (3H, m, ArH_{meta}, ArH_{para}), 5.86 (1H, dt, J=14.0, 6.0 Hz, H4), 5.64 (1H, dd, J=14.0, 4.0 Hz, H3), 4.70 (1H, m, H2), 4.58 (2H, s, O–CH_2–O), 3.99 (2H, d, J=6.0 Hz, H5), 3.31 (3H, s, O–CH_3), 3.25 (2H, m, H1); δ_C (50 MHz; $CDCl_3$) 139.5, 134.3, 131.2, 129.7 (2C), 129.0, 128.2(2C), 96.0, 66.5, 62.1, 55.5; EIHRMS: calcd for $C_{13}H_{18}O_5S$(M+Na): 309.0773; found: 309.0767 (M+Na).

*4.2.4. Oxidation of **2a** with PDC: (E)-5-(methoxymethoxy)-1-(phenylsulfonyl)pent-3-en-2-one, **3**.* A mixture of **2a** (1.08 g, 3.77 mmol) and molecular sieves was dissolved in 19 ml of DCM under Ar and stirred at rt for 5 min. PDC (2.84 g, 7.55 mmol) was added and left to stir for 3 h. The mixture was filtered through a pad of Celite®/Silica/Celite®, and then extracted with EtOAc to afford a crude brown oil. Flash chromatography (hexane/EtOAc, 6/4) afforded **3** (535 mg, 50%). ν_{max} (liquid film) 2938, 1671, 1324, 1152; δ_H (200 MHz; $CDCl_3$) 7.88 (2H, d, J=8.3 Hz, ArH_{ortho}), 7.73–7.48 (3H, m, ArH_{meta}, ArH_{para}), 6.96 (1H, dt, J=15.8, 3.9 Hz, H4), 6.55 (1H, d, J=15.8 Hz, H3), 4.66 (2H, s, O–CH_2–O), 4.31 (2H, s, H1), 4.27 (2H, d, J=3.9 Hz, H5), 3.37 (3H, s, O–CH_3); δ_C (50 MHz; $CDCl_3$) 187.1, 147.1, 138.8, 134.5, 129.5, 128.6, 128.0, 96.4, 66.0, 65.8, 55.8; EIHRMS: calcd for $C_{13}H_{16}O_5S$ (M+Na): 307.0616; found: 307.0610 (M+Na).

4.3. Typical procedure for reaction of 3 with pentenal and different catalysts and conditions (Table 1)

Compound **3** (50 mg, 17.6 mmol) and (*E*)-2-pentenal (18 μl, 17.6 mmol) were dissolved in 1 ml of the solvent used. Next, a solution of the catalyst (20 mol %), and additive (20 mol %) if needed, was added and left stirring for the appropriate time. Compounds **6a** and **6b** were isolated as a 1/1 mixture and compounds **7***E* and **7***Z* were isolated as a 2/1 mixture. From this mixture each compound **7***E* and **7***Z* was separated by flash chromatography and characterised.

4.3.1. (3R,4S*,E) and (3R*,4R*,E)-3-Ethyl-8-(methoxymethoxy)-5-oxo-4-(phenylsulfonyl)oct-6-enal, **6a** (syn)/**6b** (anti), (1/1) mixture.* Compound **6a** (*syn*)/**6b** (*anti*): ν_{max} (liquid film) 2959, 2936, 1718, 1670, 1448, 1309, 1282, 1022, 1062, 1033; δ_H (200 MHz; $CDCl_3$) 9.77 and 9.68 (1H, s, CHO), 7.88 (2H, m, Ar), 7.70–7.50 (3H, m, Ar), 6.97 (1H, dt, J=15.8, 3.9 Hz, H7), 6.57 (1H, dt, J=15.8, 2.0 Hz, H6), 4.67 (2H, s, O–CH_2–O), 4.62 (1H, m, H4), 4.31–4,16 (2H, m, H8), 3.37

(3H, s, O–CH_3), 3.20–2.40 (2H, m, H2), 1.68–1.40 (3H, m, H3 and H1′), 1.01–0.74 (3H, t, J=7.2 Hz, H2′); δ_C (50 MHz; $CDCl_3$) 200.9, 200.8, 191.5, 191.2, 145.8, 145.7, 138.5, 138.3, 134.5 (2C), 129.5 (4C), 129.2 (4C), 128.0126.7, 96.4, 96.3, 75.3, 74.1, 66.0, 65.9, 55.8(2C), 44.8, 43.3, 34.2, 33.9, 26.0, 24.4, 11.5, 11.1. EIHRMS: calcd for $C_{18}H_{22}O_5S$ (M+Na): 391.1191; found: 391.1189.

4.3.2. (5R,6S*,E)-5-Ethyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***7****E*. Compound **7***E*: ν_{max} (liquid film) 3416, 2935, 1676, 1448, 1384, 1321, 1150, 1084, 1039; δ_H (400 MHz; $CDCl_3$, HMQC, HMBC) 7.80–7.75 (2H, m, Ar), 7.60–7.45 (3H, m, Ar), 6.60 (1H, t, J=6.0 Hz, H1′), 6.45 (1H, d, J=12.0 Hz, H3), 6.10 (1H, m, H4), 4.65 (2H, s, O–CH_2–O), 4.31 (2H, d, J=6.0 Hz, H2′), 3.91 (1H, s, H6), 3.38 (3H, m, O–CH_3), 3.35 (1H, m, H5), 1.45 (2H, m, H1″), 0.85 (3H, t, J=8.0 Hz, H2″); δ_C (100 MHz; $CDCl_3$) 189.3, 137.8, 134.7, 134.1, 131.2, 130.7, 128.9 (4C), 122.5, 96.3, 75.6, 63.3, 55.7, 37.9, 29.1, 10.7; EIHRMS: calcd for $C_{18}H_{22}O_5S$ (M+Na): 373.1086; found: 373.1080. Enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; first peak t_R=22.4 min; second peak t_R=24.9 min.

4.3.3. (5R,6S*,Z)-5-Ethyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***7****Z*. Compound **7***Z*: ν_{max} (liquid film) 3416, 2935, 1676, 1448, 1384, 1321, 1150, 1084, 1039; δ_H (200 MHz; $CDCl_3$) 7.85–7.75 (2H, m, Ar), 7.65 (1H, m, Ar), 7.60–7.40 (2H, m, Ar), 6.20 (1H, d, J=10.0 Hz, H3), 6.06 (1H, t, J=6.0 Hz, H1′), 5.86 (1H, dd, J=10.0, 6.0 Hz, H4), 4.65 (2H, s, O–CH_2–O), 4.51 (1H, dd, J=16.0, 6.0 Hz, $H2_A$′), 4.43 (1H, dd, J=16.0, 10.0 Hz, $H2_B$′), 3.88 (1H, s, H6), 3.38 (3H, s, O–CH_3), 3.35 (1H, m, H5), 1.75 (2H, m, H1″), 0.65 (3H, t, J=8.0 Hz, H2″); δ_C (50 MHz; $CDCl_3$) 190.8, 137.9, 134.9, 134.5, 130.9, 130.5, 129.2 (4C), 126.7, 96.5, 77.1, 67.0, 55.6, 38.6, 28.8, 9.8; EIHRMS: calcd for $C_{18}H_{22}O_5S$ (M+Na): 373.1086; found: 373.1080. Enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; first peak t_R=18.3 min; second peak t_R=19.0 min, for the rest of spectral properties see Section 4.3.3.

4.4. Typical procedure for reaction of 3 with different aldehydes and L-proline (Table 2)

Compound **3** (50 mg, 17.6 mmol) and the corresponding aldehyde (17.6 mmol) were dissolved in 1 ml of isopropyl alcohol. Next, a solution of L-proline (20 mol %), and additive (20 mol %) if needed, was added and left stirring for the appropriate time. In this case, compounds **11**–**14** were isolated as a 2/1 mixture of diastereoisomers *E*/*Z*. When mixtures, the spectral data are indicated for the major compound.

4.4.1. (5R,6S*,E)-5-Propyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***11****E*/***11****Z*. Compound **11***E*/**11***Z*: ν_{max} (liquid film), 2940, 2931, 1676, 1384, 1310, 1150, 1084, 1038; δ_H (200 MHz; $CDCl_3$) 7.97–7.69 (2H, m, Ar), 7.67–7.42 (3H, m, Ar), 6.61 (1H, t, J=6.2 Hz, H1′), 6.42 (1H, d, J=10.2 Hz, H3), 6.05 (1H, m, H4), 4.64 (2H, s, O–CH_2–O), 4.32 (2H, d, J=6.2 Hz, H2′), 3.91 (1H, s, H6), 3.52–3.30 (1H, m, H5), 3.38 (3H, s, O–CH_3), 1.48–1.18 (4H, m, H1″, H2″), 0.87 (3H, t, J=8.0 Hz, H-2″); δ_C (50 MHz; $CDCl_3$) 189.0, 142.8, 138.0, 135.0, 134.4, 131.3, 129.5 (2C), 129.3(2C), 122.6, 96.5, 76.0, 63.7, 55.6, 38.4, 20.2, 19.8, 13.9. EIHRMS: calcd for $C_{19}H_{24}O_5S$ (M+Na): 387.1242; found: 387.1247 (M+Na).

4.4.2. (5R,6S*,E)-5-Butyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***12****E*/***12****Z*. Compound **12***E*/**12***Z*: ν_{max} (liquid film) 2957, 2932, 2872, 1281, 1138, 1124, 1097, 1043; δ_H (200 MHz; $CDCl_3$) 7.80–7.75 (2H, m, Ar), 7.60–7.49 (3H, m, Ar), 6.61 (1H, t, J=6.2 Hz, H1′), 6.42 (1H, d, J=10.3 Hz, H3), 6.03 (1H, m, H4), 4.64 (2H, s, O–CH_2–O), 4.32 (2H, d, J=6.2 Hz, H-2′), 3.91 (1H, s, H6), 3.42 (1H, m, H5), 3.38 (1H, s, O–CH_3) 1.26 (4H, m, H1″, H2″), 0.85 (3H, t, J=6.6 Hz, H2″); δ_C (50 MHz; $CDCl_3$) 189.6, 144.0, 138.0, 135.0, 134.4, 131.4, 131.4, 129.3 (3C), 122.5, 96.4, 76.1, 63.6, 55.7, 36.7, 36.1, 28.7, 22.6, 14.0. EIHRMS: calcd for $C_{13}H_{18}O_5S$ (M+Na): 401.1399; found: 401.1402 (M+Na).

4.4.3. (5R,6S*,E)-5-(3-tert-Butyldimethylsilyloxy)-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***13****E*/***13****Z*. Compound **13***E*/**13***Z*: ν_{max} (liquid film) 2955, 2932, 2887, 2858, 1375, 1281, 1174, 1140, 837; δ_H (200 MHz; $CDCl_3$) 7.80–7.75 (2H, m, Ar), 7.6–7.39 (3H, m, Ar), 6.62 (1H, t, J=6.2 Hz, H1′), 6.43 (1H, d, J=10.3 Hz, H3), 5.95–5.83 (1H, m, H4), 4.64 (2H, s, O–CH_2–O), 4.31 (2H, d, J=6.2 Hz, H2′), 3.91 (1H, s, H6), 3.55 (2H, m, H2″) 3.38 (O–CH_3), 3.35 (1H, m, H5), 1.49 (2H, m, H1″), 0.86 (9H, O–Si–*t*-Bu), −0.08 (6H, O–Si–Me_2); δ_C (50 MHz; $CDCl_3$) 189.5, 138.0, 135.1, 134.5, 131.2, 131.1, 129.3 (3C), 122.7, 96.4, 76.0, 63.6, 62.5, 55.7, 36.4, 32.9, 30.0, 26.2 (3C), 18.5, −5.1 (2C). EIHRMS: calcd for $C_{25}H_{38}O_6SSi$ (M+Na): 517.2056; found: 517.2059 (M+Na).

4.4.4. Using aldehyde ***2*** *we were able to separate the cyclisation products: (5R,6S,E)-5-(1-methoxymethoxymethyl)-2-(2′-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***14****E*. Compound **14***E*: ν_{max} (liquid film) 2938, 2889, 1699, 1448, 1321, 1281, 1151, 1039; δ_H (400 MHz; $CDCl_3$) 7.90–7.85 (2H, m, Ar), 7.73–7.40 (3H, m, Ar), 6.61 (1H, t, J=8.4 Hz, H3), 6.55 (1H, d, J=10.0 Hz, H1′), 5.93 (1H, m, H4), 4.63 (2H, s, O–CH_2–O), 4.46 (O–CH_2–O), 4.30 (2H, m, H2′), 4.13 (1H, s, H6), 3.61 (2H, m, H1″), 3.39 (1H, m, H5), 3.35 (3H, s, O–CH_3), 3.22 (3H, s, O–CH_3); δ_C (100 MHz; $CDCl_3$) 188.6, 137.9, 135.3, 134.5, 131.3, 128.6 (4C), 127.0, 125.0, 96.5, 96,3, 73.7, 69.1, 63.5, 55.7 (2C), 37.9. EIHRMS: calcd for $C_{20}H_{26}O_7S$ (M+Na): 433.1297; found: 433.1294 (M+Na).

4.4.5. (5R,6S,Z)-5-(1-Methoxymethoxymethyl)-2-(2′-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***14****Z*. Compound **14***Z*: ν_{max} (liquid film) 2937, 2889, 1448, 1375, 1309, 1281, 1149, 1109, 1037, 918; δ_H (400 MHz; $CDCl_3$) 7.90–7.85 (2H, m, Ar), 7.73–7.40 (3H, m, Ar), 6.30 (1H, d, J=10.0 Hz, H3), 6.10 (1H, t, J=5.2 Hz, H1′), 5.80 (1H, m, H4), 4.65 (2H, s, O–CH_2–O), 4.60 (O–CH_2–O), 4.60 (2H, m, H2′), 4.10 (1H, s, H6), 3.65 (2H, m, H1″), 3.41 (3H, s, O–CH_3), 3.40 (1H, m, H5), 3.25 (3H, s, O–CH_3); δ_C (100 MHz; $CDCl_3$) 189.8, 144.5, 137.9, 134.5, 130.7, 130.4, 129.3 (2C), 129.2 (2C) 124.7, 96.5(2C), 74.9, 69.1, 67,1, 55.8, 55.6, 38.4. EIHRMS: calcd for $C_{20}H_{26}O_7S$ (M+Na): 433.1297; found: 433.1292 (M+Na).

4.5. Typical procedure for reaction of 3 with catalysts 5b and L-proline in a tandem way (Table 3)

Compound **3** (50 mg, 17.6 mmol) and aldehyde (17.6 mmol) were dissolved in 1 ml of $CDCl_3$ or $CHCl_3$. Next, catalyst **5b** (20 mol %) was added and the mixture was stirred for the specified time. When the disappearance of the starting materials is observed by ^1H NMR, L-proline (20 mol %), is added and the reaction continues until the cyclic compounds are formed.

Compounds **7**–**14** were isolated as a 2/1 mixture of diastereoisomers *E*/*Z*.

Compounds **7***E* and **7***Z*, and **14***E* and **14***Z* were separated by flash chromatography.

4.5.1. We were able to separate compounds **7***E and* **7***Z from the mixture: (5R,6S,E)-5-ethyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* **7***E*. $[\alpha]_D^{22}$ −6.8 (*c* 0.3, $CHCl_3$); enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; t_R (major)=22.4 min; t_R (minor)=24.9 min, for the rest

of spectral properties see Section 4.3.2. (5*R*,6*S*,*Z*)-5-*Ethyl*-2-(2′-(*methoxymethoxy*)*ethylidene*)-6-(*phenylsulfonyl*)*cyclohex*-3-*enone*, **7***Z*. Enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; t_R (major)=18.3 min; t_R (minor)=19.0 min, for the rest of spectral properties see Section 4.3.3.

4.5.2. (5R,6S,E/Z)-5-Propyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***11****E*/***11****Z*. For a mixture 2/1 of compounds $[\alpha]_D^{22}$ −17.2 (*c* 1.1, $CHCl_3$); enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; compound **11***E*: t_R (major)=15.5 min; t_R (minor)=19.6 min; compound **11***Z*: t_R (major)=17.4 min; t_R (minor)=21.5 min; for the rest of spectral properties see Section 4.4.1.

4.5.3. (5R,6S,E/Z)-5-Butyl-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***12****E*/***12****Z*. For a mixture 2/1, $[\alpha]_D^{22}$ −14.5 (*c* 1.1, $CHCl_3$); we were able to separate a small amount of compound **12***E*. $[\alpha]_D^{22}$ −13.0 (*c* 0.2, $CHCl_3$). Enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; compound **12***E* t_R (major)=16.9 min; t_R (minor)=14.2 min; compound **12***Z* t_R (major)=14.8 min; t_R (minor)=13.6 min. For the rest of spectral properties see Section 4.4.2.

4.5.4. (5R,6S,E/Z)-5-(3-tert-Butyldimethylsilyloxy)-2-(2′-(methoxymethoxy)ethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***13****E*/***13****Z*. For a mixture 2/1, $[\alpha]_D^{22}$ −27.5 (*c* 0.6, $CHCl_3$); enantiomeric ratio determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90/10 (v/v)]; flow rate: 1.0 mL/min; λ=218 nm; compound **13***E* t_R (major)=10.2 min; t_R (minor)=11.8 min; compound **13***Z* t_R (major)=9.1 min; t_R (minor)=10.5 min. For the rest of spectral properties see Section 4.4.3.

4.5.5. Using the aldehyde ***2*** *we were able to separate the cyclisation products: (5R,6S,E)-5-(1-methoxymethoxymethyl)-2-(2′-methoxy methoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone,* ***14****E*. $[\alpha]_D^{25}$ +0.97 (*c*1.9, $CHCl_3$). For the rest of spectral properties see Section 4.4.4.

4.5.6. (5R,6S,Z)-5-(1-Methoxymethoxymethyl)-2-(2′-methoxymethoxyethylidene)-6-(phenylsulfonyl)cyclohex-3-enone, ***14****Z*. $[\alpha]_D^{25}$ −7.57 (*c* 0.8, $CHCl_3$). For the rest of spectral properties see Section 4.4.5.

In this case we were unable to determine the enantiomeric ratio of the compounds.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.08.068. These data include MOL files and InChiKeys of the most important compounds described in this article.

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