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Enantioselective aldol reactions with aqueous 2,2-dimethoxyacetaldehyde organocatalyzed by binam-prolinamides under solvent-free conditions

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Fernando J. N. Moles, Abraham Bañón-Caballero, Gabriela Guillena,* and Carmen Nájera*

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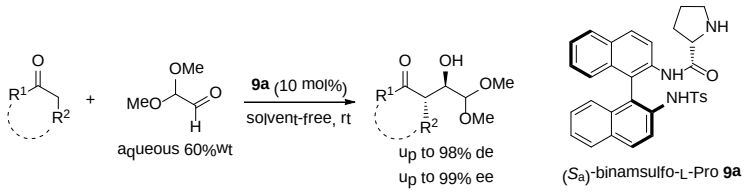

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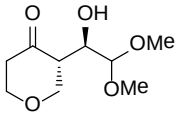

$C_9H_{16}O_5$

(S)-3-((R)-1-Hydroxy-2,2-dimethoxyethyl)dihydro-2H-pyran-4(3H)-one

Source of chirality: (S_a)- Binam and L-Pro

$[\alpha]_D^{20} = -18$ (*c* 0.8, $CHCl_3$, 95% *ee* from GC)

Absolute configuration: (*S*,3*R*)

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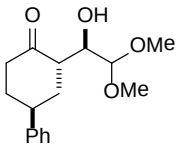

$C_{16}H_{22}O_4$

(2S,4S)-2-((R)-1-Hydroxy-2,2-dimethoxyethyl)-4-phenylcyclohexanone

Source of chirality: (S_a)-Binam and L-Pro

$[\alpha]_D^{20} = -40$ (*c* 1.6, $CHCl_3$, 97 % *ee* from HPLC)

Absolute configuration: (*R*,2*S*,4*S*)

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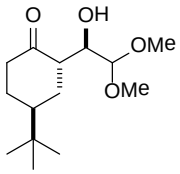

$C_{14}H_{26}O_4$

(2S,4S)-4-(tert-Butyl)-2-((R)-1-hydroxy-2,2-dimethoxyethyl)-cyclohexanone

Source of chirality: (S_a)-Binam and L-Pro

$[\alpha]_D^{20} = -100$ (*c* 3, $CHCl_3$, 95% *ee* from GC)

Absolute configuration: (*R*,2*S*,4*S*)

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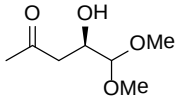

$C_7H_{14}O_4$

(R)-4-Hydroxy-5,5-dimethoxypentan-2-one

Source of chirality: (S_a)-Binam and L-Pro

$[\alpha]_D^{20} = -35$ (*c* 0.8, $CHCl_3$, 99% *ee* from GC)

Absolute configuration: (*R*)

Pergamon

TETRAHEDRON:
ASYMMETRY

Enantioselective aldol reactions with aqueous 2,2-dimethoxyacetaldehyde organocatalyzed by binam-prolinamides under solvent-free conditions

Fernando J. N. Moles, Abraham Bañón-Caballero, Gabriela Guillena,* and Carmen Nájera*

Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo 99, 03080 Alicante, Spain

Abstract— Aqueous 2,2-dimethoxyacetaldehyde (60%wt solution) is used as acceptor in aldol reactions, with cyclic and acyclic ketones and aldehydes as donors, organocatalyzed by 10 mol% of *N*-tosyl-(S_a)-binam-L-prolinamide [(S_a)-binam-sulfo-L-Pro] at rt under solvent-free conditions. The corresponding monoprotected 2-hydroxy-1,4-dicarbonyl compounds are obtained in good yields and high levels of diastero- and enantioselectivity mainly as *anti*-aldols. In the case of 4-substituted cyclohexanones a desymetrization process takes place affording mainly the *anti,anti*-aldols. 2,2-Dimethyl-1,3-dioxan-5-one allows the synthesis of a useful intermediate for the preparation of carbohydrates in higher yield, de and ee than with L-Pro as organocatalyst.

1. Introduction

Organocatalyzed direct aldol reactions has became a fundamental reaction in asymmetric synthesis.[1] Since the pioneering work of List[2] using L-proline as catalysts for intermolecular aldol reactions a plethora of organocatalysts under several reaction conditions have been developed.[3] The scope of ketones and aldehydes as donors and electrophiles has been extensively studied. Of special interest is the use of glyoxal dimethyl acetal as acceptor for the direct access to monoprotected 2-hydroxy-1,4-dicarbonyl compounds. This synthetic equivalent to protected glyoxal is available as 60%wt solution in water and has been used directly in biomimetic organocatalyzed asymmetric synthesis of carbohydrates by means of aldol reactions.[4] However, few examples using this aldehyde as acceptor has been described. For the aldehyde-ketone aldol reaction,[4a-i] L-Pro in DMF[4a,b] or in DMSO,[4c,d] *O-tert*-Bu-L-threonine (**1**)[4e] in NMP and its derivative **2**,[4f] primary amines such as the *trans*-cyclohexane-1,2-diamine derived catalyst **3** with TfOH[4g] and **4** with $H_3PW_{12}O_{40}$[4h] have been used as catalysts (Figure 1). Hayashi et al. used L-Pro under solvent free conditions[4i] with moderate to high diastero and enantioselectivity. On the other hand, for the aldehyde-aldehyde aldol reaction using glyoxal dimethyl acetal as acceptor,[4j-m] different organocatalysts such as 4-hydroxy-L-proline derivative **5** in water,[4j] the diarylproplinol **6**[4k] in DMF and L-histidine in water[4l,m] have been employed (Figure 1). In addition, L-Pro under solvent-free conditions has been also used for the aldol reaction of phenylpropanal.[4i]

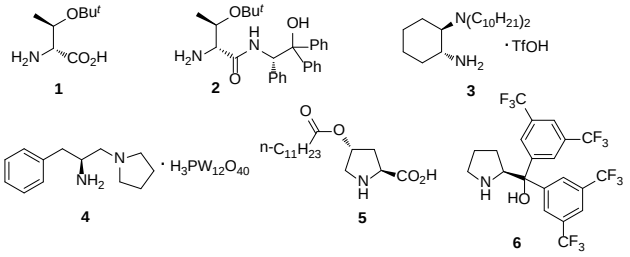

Figure 1. Organocatalysts used in aldol reactions with 2,2-dimethoxyacetaldehyde.

Our research group and also others have found that (S_a)-binam-derived prolinamides **7**-**10** and their enantiomers[5,6] have shown good catalytic activity in inter and intramolecular aldol reactions in organic solvents, in aqueous media and specially under solvent-free[7] conditions (Figure 2). Prolinamides **7** and **8** have been used as recoverable catalysts in intermolecular aldol reactions by simple extractive acid-base work-up.[5] On the other hand, *N*-tosyl-(S_a)-binam-L-prolinamides [(S_a)-binam-sulfo-L-Pro] **9a** and **10a** have shown their

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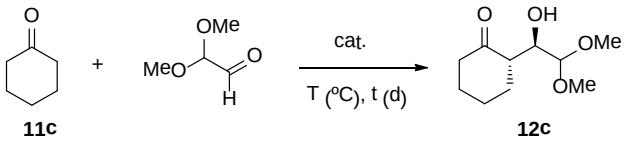
efficiency as general organocatalysts for inter- and intramolecular aldol reactions in water and under solvent-free conditions.[6a-d] However, in order to recover and to reuse them, they have covalently supported to polymers **9b** and **10b**[6e] and also **9c** and **10c**[6f] or in silica gel **9d** and **10d**[6g] (Figure 2). We report in this paper the application of binam-prolinamides as catalysts for the direct asymmetric aldol reaction of 2,2-dimethoyacetaldehyde with different carbonyl compounds for the enantioselective and general synthesis of 2-hydroxy-1,4-dicarbonyl compounds.

2. Results and discussion

Initial attempts were carried out using commercially available aqueous 60%wt solution of 2,2-dimethoxyacetaldehyde with 10 equiv of cyclohexanone (**11c**) and 20 mol% of the organocatalyst at rt under conventional magnetic stirring (Scheme 1 and Table 1). By using (S_a)-binam-L-Pro **7,** the *anti*-aldol **12c** was obtained quantitatively with 91% de and 88% ee after 1 d reaction time (Table 1, entry 1). The absolute configuration of **12c** was assigned according to the data of the same compound prepared by using L-Pro as catalyst.[4i] Diasteromeric catalyst (S_a)-binam-D-Pro **8** afforded *ent*-**12c** in poorer results, 88% de and 72% ee, than **7** (Table 1, entry 2).



Scheme 1. Aldol reaction between cyclohexanone and 2,2-dimethoxyacetaldehyde

Table 1

Screening and optimization of the reaction conditions for the enantioselective aldol reaction of **11c** and 2,2-dimethoxyacetaldehyde.

Ent.	Cat. (mol%)	**11c** (eq.)	Additive (5 mol%)	*T* (ºC)	*t* (d)	Conv[a] (%)	Yield[b] (%)	de[c]	ee[d] (%)
1	**7** (20)	10	-	25	1	100	-	91	88
2	**8** (20)	10	-	25	1	100	-	88	72[e]
3	**9a** (20)	10	-	25	1	90	80	96	97
4	**10a** (20)	10	-	25	1	75	63	92	91[e]
5	**9a** (20)	5	-	25	1	100	-	93	97
6	**9a** (20)	2	-	25	1	100	-	92	98
7	**9a** (10)	2	-	25	1	88	78	99	97
8	**9a** (5)	2	-	25	1	75	-	96	97
9	**9b** (10)	2	-	25	7	-	-	-	-
10	**9d** (10)	2	-	25	7	-	-	-	-
11	**L-Pro** (10)	2	-	25	2	75	60	80	84
12	**9a** (10)	2	-	0	2	100	82	97	98
13	**9a** (5)	2	$PhCO_2H$	25	1	75	-	94	95
14	**9a** (5)	2	4-NO_2-$C_6H_4CO_2H$	25	1	69	-	96	93
15	**9a** (5)	2	AcOH	25	1	73	-	96	94
16	**9a** (5)	2	Cl_2CHCO_2H	25	1	71	-	95	94

[a] Determined by ^{1}H NMR (300 MHz).
[b] Isolated yield after column chromatography based on 2,2-dimethoxyacetaldehyde (0.25 mmol).
[c] *anti/syn* Diasteromers, determined by ^{1}H NMR (300 MHz).
[d] Determined by GC with a chiral column CP CHIRALSIL DEX CB.
[e] *ent*-**12c** was obtained.

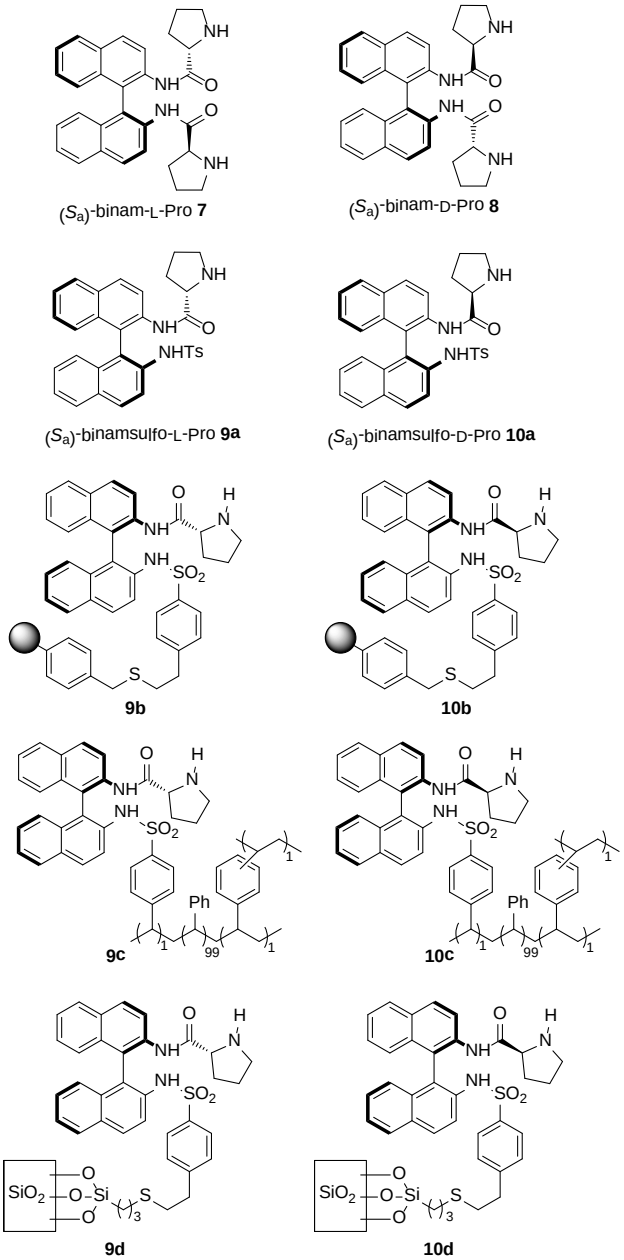


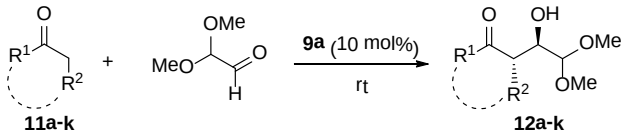
Figure 2. Binam-derived organocatalysts.

In the case of (S_a)-binam-sulfo-L-Pro **9a** and D-Pro **10a** *anti*-**12c** was obtained after 1 d in 80 and 63% isolated yield, respectively, giving **9a** the best sterochemical results for **12c**, 96% de and 97% ee (Table 1, entries 3 and 4, respectively). Whereas, *ent*-**12a** was obtained in lower 92% de and 91% ee using organocatalyst **10a** (Table 1, entry 4).

For the screening of the stoichiometry of the reaction **9a** was used as organocatalyst showing that the amount of cyclohexanone (**11c**) could be reduced to 2 equiv giving full conversion and similar sterochemical results (Table 1, compare entries 3 and 6). When the catalyst loading was reduced to 10 and 5 mol% lower conversions were observed but with similar sterochemical results than with 20 mol% (Table 1, entries 7 and 8). Unfortunately, using supported catalysts **9b** and **9d** (10 mol%) and 2 equiv of **11a** for 7 d, the reaction failed (Table 1, entries 9 and 10). Under the same reaction conditions L-Pro afforded lower chemical yield (60%) and sterochemical results (80% de, 84% ee) than with **9a** (Table 1, compare entries 7 and 11). In the case of Hayashi's conditions, *anti*-**12c** was obtained, after 92 h reaction time and using 5 equiv of **11c** and 30 mol% of L-Pro, in 80% yield as a 10:1 diasteromer ratio and 93% ee.[4i]

The influence of the reaction temperature was then determined. Thus, when the temperature was lowered down to 0 ºC the enantioselection for *anti*-**12c** remained essentially the same than when working at 25 ºC, but the reaction time increased form 1 to 2 d (Table 1, entry 12). The effect of acids as additives was studied with 5 mol% of catalyst **9a** and 5 mol% loading of benzoic, 4-nitrobenzoic, acetic and dichloroacetic acids (Table 1, entries 13-16). In general similar results were obtained than without additive (Table 1, compare entry 8 with entries 13-16).

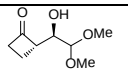
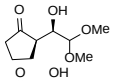
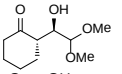
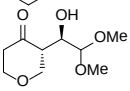
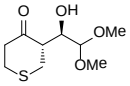
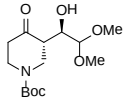
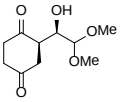
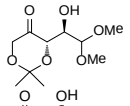
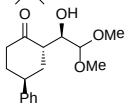
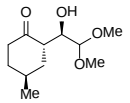
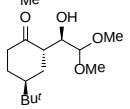
The scope of the aldol reaction with different cyclic ketones (2 equiv) were performed with **9a** (10 mol%) at rt (Scheme 2 and Table 2). Cyclobutanone (**11a**) showed a lower diastereoselectivity than cyclohexanone affording *anti*-**12a** in 34% de and modest 50% yield, although in 97% ee (Table 2, entry 1). On the other hand, cyclopentanone (**11b**) afforded as usual mainly *syn*-**12b** in 62% de, higher than the 0% de obtained under L-Pro catalysis.[4i] The *syn*-aldol **12b** was obtained in similar 95% ee than with L-Pro (93%)[1i] (Table 2, entry 2). In the case of 6-membered cycloalkanones **11c-11f,** products **12c-12f** were obtained mainly as *anti*-isomers in high yields, diastero and enantioselectivities (Table 2, entries 3-6). However, cyclohexane-1,4-dione (**11g**) the corresponding *syn*-**12g** was mainly obtained in 48% de and in 96% ee (Table 2, entry 7).



Scheme 2. Aldol reaction between cycloalkanones and 2,2-dimethoxyacetaldehyde.

In the case of using the protected 1,3-dihydroxyacetone, 2,2-dimethyl-1,3-dioxan-5-one (**11h**), the protected D-erythro- pentos-4-ulose (**12h**) was obtained in 96% de and 92% ee (Table 2, entry 8). For comparison L-Pro (30 mol%) gave, after 13 h reaction time, **12h** in 47% yield, 90% de and 83% ee under the same solvent-free conditions.[4i] Whereas, L-Pro (30 mol%) in DMF at 2 ºC gave **12h** in 69% yield, 88% de and 90% ee.[4a] Under similar reaction conditions using L-Pro (20 mol%) but at 4 ºC, **12h** was obtained in 60% yield, 18:1 dr and 98% ee.[4b] Similar results, 60% yield, 84% de and 96% ee have been obtained using dry DMSO at 5 ºC in the presence of LiCl.[4d] When 4-substituted cyclohexanones **11i-k** were used as donors a concomitant desymetrization took place giving mainly *anti*,*anti*-aldols **12i-k** in high yields, de and ee (Table 2, entries 9-11).

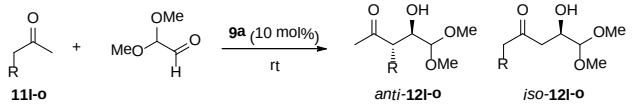
Table 2
Enantioselective aldol reaction of cyclic ketones and 2,2-dimethoxyacetaldehyde catalyzed by (S_a)-binam-sulfo-L-Pro **9a**[a]

Entry	Product	No.	*t* (h)	Yield[b] (%)	dr[c]	ee[d,e] (%)
1		**12a**	48	50	67:33	97
2		**12b**	48	74	14:86	95
3		**12c**	32	87	98:2	97
4		**12d**	50	82	97:3	95
5		**12e**	50	73	91:9	92
6		**12f**	48	66	99:1[e]	92[e]
7		**12g**	48	81	26:74	96
8		**12h**	48	68	98:2	92
9		**12i**	52	80	95:3:2:1	97[f]
10		**12j**	48	92	94:4:1:1	96
11		**12k**	48	93	96:2:1:1	95

[a] Reaction conditions: 60%wt aqueous 2,2-dimethoxyacetaldehyde (0.25 mmol), cycloalkanone (0.5 mmol) and **9a** (10 mol%) at rt.
[b] Isolated yield after column chromatography based on 2,2-dimethoxyacetaldehyde.
[c] *anti/syn* Diasteromers, determined by ^{1}H NMR (300 MHz).
[d] Determined by GC with a chiral column CP CHIRALSIL DEX CB.
[e] For the major diastereomer.
[f] Determined by HPLC with a chiral column Chiralpak IA.

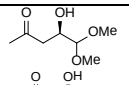
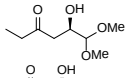
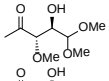
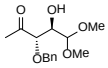
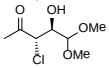
Acyclic ketones **11l-p** were allowed to react with 2,2-dimethoxyacetaldehyde under the same reaction

conditions to give aldols **12l-p** (Scheme 3, Table 3). Acetone (**11l**) gave aldol **12l** in high 99% ee and moderate 55% yield (Table 3, entry 1). In the case of butan-2-one (**11m**), a 1:9 mixture of regioisomers **12m** were obtained (Table 3, entry 2). The major *iso*-isomer was isolated in 48% yield and in 95% ee. When α-alkoxyacetones **11n** and **11o** were allowed to react with 2,2-dimethoxyacetaldehyde, *anti*- and *iso*-aldols **12n** and **12o** were obtained as 2:1 and 1:1 regiosiomeric mixtures, respectively (Table 3, entries 3 and 4). The *anti*-aldols **12n** and **12o** were isolated in 82 and 90% de, respectively, and in 90 and 94% ee. A higher regioselectivity was observed in the case of α-chloroacetone (**11p**) affording aldol **12p** as a 9:1 mixture of *anti:iso* regioisomers (Table 3, entry 5). The major *anti*-isomer **12p** was isolated in 80% de and in 97% ee.



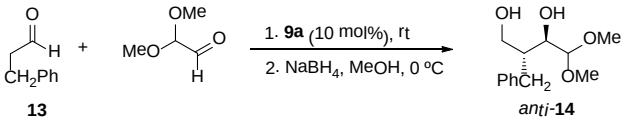
Scheme 3. Aldol reaction between acyclic ketones and 2,2-dimethoxyacetaldehyde.

Table 3
Enantioselective aldol reaction of acyclic ketones and 2,2-dimethoxyacetaldehyde catalyzed by (S_a)-binam-sulfo-L-Pro **9a**[a]

Ent.	Product	No.	*t* (d)	Yield[b] (%)	*anti:iso*[c]	de[c,d]	ee[e,f] (%)
1		**12l**	3	55	.	-	99
2		**12m**	4	48	10:90	-	95
3		**12n**	4	30	68:32	82	90
4		**12o**	4	49	58:42	90	94[g]
5		**12p**	4	53	90:10	80	97

[a] Reaction conditions: 60%wt aqueous 2,2-dimethoxyacetaldehyde (0.25 mmol), alkanone (0.5 mmol) and **9a** (10 mol%) at rt.
[b] Isolated yield after column chromatography based on 2,2-dimethoxyacetaldehyde..
[c] Determined by ^{1}H NMR (300 MHz).
[d] *anti/syn* Diasteromers.
[e] Determined by GC with a chiral column CP CHIRALSIL DEX CB.
[f] For the major diastereomer.
[g] Determined by HPLC with a chiral column Chiralpak IA.

The aldol reaction with a representative aldehyde, 3-phenylpropanal (**13**), afforded the corresponding aldol after 72 h reaction time, which was submitted to subsequent reduction with $NaBH_4$ giving rise the diol **14** in 64% yield as a mixture 4:1 of *anti/syn* diasteromers and in 97% ee for the *anti*-**14** product (determined by HPLC) (Scheme 4). The same reaction catalyzed by L-Pro gave product **14** in 40% yield as a 3.3:1 *anti/syn* mixture and the *anti*-**14** in 92% ee.[4i]



Scheme 4. Aldol reaction between 3-phenylpropanal (**13**) and 2,2-dimethoxyacetaldehyde.

3. Conclusions

It can be concluded that binam-prolinamides can be used as chiral catalysts to perform the aldol reaction of 2,2-dimethoxyacetaldehyde as acceptor with cyclic and acyclic ketones as well as aldehydes under solvent-free conditions, just in the presence of 3.8 equiv of water from the aqueous 60%wt 2,2-dimethoxyacetaldehyde. From the assayed unsupported and supported binam-derived organocatalysts, (S_a)-binam-sulfo-L-prolinamide has shown the highest efficiency for this type of aldol reaction better than the previous described reactions with L-Pro under the same solvent-free conditions.

4. Experimental

4.1. General

Catalysts **7-10** were prepared according to literature.[2,3] All the reagents were commercially available and used without further purification. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained at 25 ºC using $CDCl_3$ as solvent and chemical shifts are reported as δ values relative to TMS as internal standard. IR spectra were obtained with Jasco 4100 LE (Pike Piracle ATR). High resolution mass spectra (HRMS-ESI) were obtained on a Waters LCT Premier XE apfortus equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatography (UPLC) model Waters ACQUITY H CLASS. Optical rotations were measured on a Jasco P-1030 polarimeter with a 5 cm cell (c given in g/100 mL). GC analyses were performed on an Agilent Technologies 7820 GC System. HPLC analyses were performed on equipped with a chiral columns Chiralpak IA and Chiralpak AD-H, and automatic injector Agilent 1100, using mixtures of n-hexane/isopropyl alcohol (IPA) as mobile phase, at 25 ºC. Analytical TLC was performed on silica gel plates and the spots were visualized using $KMnO_4$ solution. For flash chromatography we employed silica gel 60 (0.040-0.063 mm). The absolute configuration of aldols **12b,c,h** and diol **14** was assigned according to the literature data[4i] and the rest of aldols by analogy with the $[\alpha]_D^{26}$ values.

4.2. General procedure for the aldol reaction

To a mixture of the 2,2-dimethoxyacetaldehyde 60%wt aqueous solution (0.038 mL, 0.25 mmol) and organocatalyst **9a** (10 mol%) at rt was added the

corresponding carbonyl compound (0.5 mmol). The reaction was stirred until the 2,2-dimethoxyacetaldehyde was consumed (monitored by TLC). The resulting residue was purified by column chromatography on silica gel (hexanes/EtOAc) to yield the pure aldol product.

4.2.1. (*S*)-2-((*R*)-1-Hydroxy-2,2-dimethoxyethyl)cyclobutanone 12a

Colorless oil (21 mg, 50%); $[\alpha]_D^{26} = -5$ (*c* 0.5, $CHCl_3$, *anti/syn*: 67/33, ee_{anti} 97% from GC); $R_f = 0.32$ (Hex/EtOAc: 1/1). IR: ν 3642 (OH), 1579 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 4.55 (d, *J* = 7.1 Hz, 1H), 3.74 (dd, *J* = 7.0, 4.1 Hz, 1H), 3.68–3.53 (m, 1H), 3.48 (s, 3H), 3.48 (s, 3H), 3.06– 2.95 (m, 2H), 2.24–2.05 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, diastereomer mixture (60:40): δ 210.3, 207.4, 105.1, 104.6, 77.2, 76.6, 70.5, 68.4, 61.4, 60.8, 56.1, 55.0, 45.9, 45.6, 13.3, 11.6. HRMS calculated for $C_8H_{14}O_4$: 174.0892; found: 197.0790(M^+ + Na, recalculated 197.0790). GC: CP CHIRALSIL DEX CB column (140 ºC, 13.4 Psi), R_t = 11.1 min (minor *anti*), R_t = 11.5 min (major *anti*), R_t = 19.6 min *(syn*).

4.2.2. (*R*)-2-((*R*)-1-Hydroxy-2,2-dimethoxyethyl)cyclopentanone 12b[4i]

Yellow oil (35 mg, 74%); %); $[\alpha]_D^{26} = -50$ (*c* 3, $CHCl_3$, *anti/syn*: 14/86, ee_{syn} 95% from GC); R_f = 0.34 (Hex/EtOAc: 1/1). IR: ν 3555 (OH), 1623 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 4.30 (d, *J* = 6.8 Hz, 1H), 4.19 (dd, *J* = 6.6, 3.5 Hz, 1H), 3.48 (d, *J* = 3.0 Hz, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 2.44–2.26 (m, 2H), 2.19–2.03 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.0, 105.0, 68.9, 54.5, 50.1, 38.6, 22.9, 20.8. MS (EI) *m/z* (%) for $C_9H_{16}O_4$: M^+ = 188 (3), 157 (10), 125 (10), 75 (100).
GC: CP CHIRALSIL DEX CB column (140 ºC, 13.4 Psi), R_t = 21.3 min (*anti*), R_t = 34.4 min (minor *syn*), R_t = 36.8 min *(*major *syn*).

4.2.3. (*S*)-2-((*R*)-1-Hydroxy-2,2-dimethoxyethyl)cyclohexanone 12c[4i]

Colorless oil (44 mg, 87%); %); $[\alpha]_D^{26} = -12$ (*c* 0.5, $CHCl_3$, *anti/syn*: 98/2, ee_{anti} 97% from GC); R_f = 0.37 (Hex/EtOAc: 1/1). IR: ν 3473 (OH), 1699 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ. 4.51 (d, *J* = 5.7 Hz, 1H), 3.63 (dd, *J* = 11.3, 5.6 Hz, 1H), 3.47 (s, 3H), 3.42 (s, 3H), 3.24 (d, *J* = 7.4 Hz, 1H), 2.71 (ddd, *J* = 9.9, 7.2, 4.4 Hz, 1H), 2.45–2.31 (m, 2H), 2.19–2.05 (m, 2H), 1.98–1.87 (m, 1H), 1.87–1.67 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.0, 105.4, 73.0, 55.7, 54.4, 51.4, 43.0 (CH_2), 31.6 (CH_2), 27.9 (CH_2), 24.9 (CH_2). MS (EI) *m/z* (%) for $C_{10}H_{18}O_4$: M^+ = 202 (5), 184 (8), 139 (12), 75 (100). GC: CP CHIRALSIL DEX CB column (160 ºC, 13.4 Psi), R_t = 5.9 min (minor. *anti*), R_t = 6.1 min (major *anti*), R_t = 6.9 min *(syn*).

4.2.4. (*S*)-3-((*R*)-1-Hydroxy-2,2-dimethoxyethyl) dihydro-2*H*-pyran-4(3*H*)-one 12d

Colorless oil (42 mg, 82%); $[\alpha]_D^{26} = -18$ (*c* 0.8, $CHCl_3$, *anti/syn*: 97/3, ee_{anti} 95% from GC); R_f = 0.22 (Hex/EtOAc: 1/1). IR: ν 3458 (OH), 1710 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 4.49 (d, *J* = 5.7 Hz, 1H), 4.18–4.07 (m, 2H), 3.86–3.78 (m, 2H), 3.75 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.06 (d, *J* = 5.2 Hz, 1H), 2.91–2.81 (m, 1H), 2.64–2.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.9, 105.4, 70.5, 70.0, 68.1, 55.9, 54.6, 52.7, 43.0. HRMS calculated for $C_9H_{16}O_5$: 204.0998; found: 227.0894 (M^+ + Na, recalculated 227.0895). GC: CP CHIRALSIL DEX CB column (130 ºC, 13.4 Psi), R_t = 25.9 min (minor *anti*), R_t = 26.3 min (major *anti*), R_t = 31.8 min (minor *syn*), R_t = 32.8 min *(*major *syn*).

4.2.5. (*S*)-3-((*R*)-1-Hydroxy-2,2-dimethoxyethyl) dihydro-2*H*-thiopyran-4(3*H*)-one 12e

Yellow oil (40 mg, 73%); $[\alpha]_D^{26} = -47$ (*c* 3.8, $CHCl_3$, *anti/syn*: 91/9, ee_{anti} 97% from GC); R_f = 0.29 (Hex/EtOAc: 1/1). IR: ν 3460 (OH), 1704 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 4.49 (d, *J* = 5.5 Hz, 1H), 3.90 (dd, *J* = 10.2, 6.8 Hz, 1H), 3.47 (s, 3H), 3.45 (s, 3H), 3.09–3.04 (m, 2H), 3.05–2.96 (m, 2H), 2.95 (d, *J* = 6.8 Hz, 1H), 2.83–2.72 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.3, 105.6, 72.1, 55.8, 54.7, 53.9, 44.6, 33.4, 30.6. HRMS calculated for $C_9H_{16}O_4S$: 220.0769; found: 243.0657 (M^+ + Na, recalculated 243.0667). GC: CP CHIRALSIL DEX CB column (160 ºC, 13.4 Psi), R_t = 34.6 min (minor *anti*), R_t = 35.5 min (major *anti*).

4.2.6. (*S*)-*tert*-Butyl-3-((*R*)-1-hydroxy-2,2-dimethoxyethyl)-4-oxopiperidin-1-carboxylate 12f

Colorless oil (55 mg, 66%); $[\alpha]_D^{26} = -20$ (*c* 1.2, $CHCl_3$, *anti/syn*: 99/1, ee_{anti} 92% from GC); R_f = 0.2 (Hex/EtOAc: 1/1). IR: ν 3435 (OH), 1689 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 4.52 (d, *J* = 5.6 Hz, 1H), 4.05 (dd, *J* = 13.5, 5.7 Hz, 1H), 3.79–3.65 (m, 2H), 3.47– 3.39 (m, 8H), 3.00–2.84 (m, 1H), 2.80–2.68 (m, 1H), 2.57–2.37 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0, 154.6, 80.5, 70.8, 55.9, 54.7, 54.4, 51.1, 43.1, 41.4, 41.1, 28.3. HRMS calculated for $C_{14}H_{25}NO_6$: 303.1682; found: 326.1581 (M^+ + Na, recalculated 326.1580). HPLC: Chiralpak IA column (98% hexane, 2% Pr^iOH, 25ºC, 1 mL/min, 230 nm), R_t = 30.0 min (major *anti*), R_t = 33.6 min (*syn*), R_t = 40.3 min (minor *anti*).

4.2.7. (*R*)-2-((*R*)-1-Hydroxy-2,2-dimethoxyethyl)cyclohexane-1,4-dione 12g

Brown oil (43 mg, 81%); $[\alpha]_D^{26} = -18$ (*c* 1.2, $CHCl_3$, *anti/syn*: 26/74, ee_{syn} 96% from GC); R_f = 0.35 (Hex/EtOAc: 1/1). IR: ν 3429 (OH), 1707 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 4.57 (d, *J* = 6.8 Hz, 1H), 4.28 (dd, *J* = 15.7, 6.8 Hz, 1H), 3.76 (dt, *J* = 6.6, 3.2 Hz, 1H), 3.47–3.42 (m, 6H), 3.00–2.59 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$, diastereomer mixture 1:1): δ 209.7, 208.6, 104.9, 104.1, 73.2, 69.6, 56.0, 55.0, 54.8, 54.7, 47.1, 47.0,

37.9, 37.4, 37.1, 36.1, 36.0. HRMS calculated for $C_{10}H_{16}O_5$: 216.0998; found: 239.0839 (M^+ + Na, recalculated 239.0837). GC: CP CHIRALSIL DEX CB column (180 ºC, 13.4 Psi), R_t = 21.4 min (minor *anti*), R_t = 5.8 min (major *syn*), R_t = 24.7 min (minor *syn*), R_t = 25.3 min *(*major *anti*).

4.2.8. (*S*)-4-((*R*)-1-Hydroxy-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-one 12h[4i]

Colorless oil (39 mg, 68%); $[\alpha]_D^{26}$ = –12 (*c* 0.6, $CHCl_3$, *anti/syn*: 98/2, ee_{anti} 92% from GC); R_f = 018 (Hex/EtOAc: 1/1). IR: ν 3449 (OH), 1748 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.68 (d, *J* = 6.8 Hz, 1H), 4.49 (dd, *J* = 13.9, 1.3 Hz, 1H), 4.36–3.92 (m, 4H), 3.50– 3.44 (m, 6H), 1.50 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 103.2, 76.0, 71.1, 67.0, 55.3, 54.3, 25.3, 24.9, 22.9. MS (EI) *m/z* (%) for $C_{10}H_{16}O_6$: M^+ = 54 (3), 219 (5), 171 (10), 129 (15), 75 (100). GC: CP CHIRALSIL DEX CB column (150 ºC, 13.4 Psi), R_t = 9.1 min (major *anti*), R_t = 9.8 min (minor *anti*), R_t = 17.8 min (minor *syn*), R_t = 18.9 min *(*major *syn*).

4.2.9. (2*S*,4*S*)-2-((*R*)-1-Hydroxy-2,2-dimethoxyethyl)-4-phenylcyclohexanone 12i

Colorless oil (55 mg, 80%); $[\alpha]_D^{26}$ = –40 (*c* 1.6, $CHCl_3$, dr: 95/3/2/1, ee_{anti} 97% from HPLC); R_f = 0.36 (Hex/EtOAc: 1/1). IR: ν 3439 (OH), 1704 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.17 (m, 5H), 4.34 (d, *J* = 6.0 Hz, 1H), 3.89 (dd, *J* = 5.2, 4.7 Hz, 1H), 3.50 (s, 3H), 3.49 (s, 3H), 3.44–3.35 (m, 1H), 2.83–2.76 (m, 1H), 2.72 (d, *J* = 4.1 Hz, 1H), 2.69–2.62 (m, 1H), 2.56–2.47 (m, 1H), 2.28–2.02 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.1, 144.6, 128.6, 126.8, 126.4, 105.7, 73.4, 56.1, 55.2, 49.7, 41.0, 38.0, 37.0, 32.8. HRMS calculated for $C_{16}H_{22}O_4$: 278.3435; found: 279.1592 (M^+ + H, recalculated 279.1596). HPLC: Chiralpak IA column (98% hexane, 2% Pr^iOH, 25ºC, 1 mL/min, 210 nm), R_t = 24.7 min (minor *anti*), R_t = 26.4 min (major *anti*).

4.2.10. (2*S*,4*S*)-2-((*R*)-1-Hydroxy-2,2-dimethoxyethyl)-4-methylcyclohexanone 12j

Colorless oil (49 mg, 92%); $[\alpha]_D^{26}$ = –80 (*c* 2.5, $CHCl_3$, dr: 94/4/1/1, ee_{anti} 96% from GC); R_f = 0.4 (Hex/EtOAc: 1/1). IR: ν 3489 (OH), 1738 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.36 (d, *J* = 5.9 Hz, 1H), 3.68 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 2.87 (d, *J* = 5.7 Hz, 1H), 2.72 (dd, *J* = 12.5, 6.1 Hz, 1H), 2.48–2.33 (m, 2H), 2.24–2.11 (m, 1H), 2.08–1.88 (m, 2H), 1.74–1.51 (m, 2H), 1.08 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.4, 105.4, 73.1, 57.7, 54.8, 48.3, 39.7, 37.7, 33.8, 27.1, 19.7. HRMS calculated for $C_{11}H_{20}O_4$: 216.1362; found: 239.1248 (M^+ + Na, recalculated 239.1259). GC: CP CHIRALSIL DEX CB column (120 ºC, 13.4 Psi), R_t = 50.7 min (minor), R_t = 51.9 min (major).

4.2.11. (2*S*,4*S*)-4-(*tert*-Butyl)-2-((*R*)-1-hydroxy-2,2-dimethoxyethyl)-cyclohexanone 12k

Colorless oil (60 mg, 93%); $[\alpha]_D^{26}$ = –100 (*c* 3, $CHCl_3$, dr: 96/2/1/1, ee_{anti} 95% from GC); R_f = 0.31 (Hex/EtOAc: 1/1). IR: ν 3439 (OH), 1703 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.30 (d, *J* = 5.7 Hz, 1H), 3.79 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.44 (s, 6H), 2.74 (d, *J* = 4.9 Hz, 1H), 2.65 (dd, *J* = 10.4, 5.2 Hz, 1H), 2.47–2.34 (m, 2H), 2.06–1.92 (m, 2H), 1.72–1.61 (m, 2H), 1.54–1.41 (m, 1H), 0.88 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.7, 105.8, 72.6, 55.9, 55.0, 49.5, 42.2, 40.6, 32.6, 29.6, 27.3, 26.0. HRMS calculated for $C_{14}H_{26}O_4$: 258.1831; found: 281.1725 (M^+ + Na, recalculated 281.1729). GC: CP CHIRALSIL DEX CB column (150 ºC, 13.4 Psi), R_t = 69.3 min (major), R_t = 71.6 min (minor).

4.2.12. (*R*)-4-Hydroxy-5,5-dimethoxypentan-2-one 12l

Colorless oil (22 mg, 55%); $[\alpha]^{26}_D$ = **–**35 (c 0.8; $CHCl_3$, ee 99% from GC); R_f = 0.3 (Hex/EtOAc: 1/1). IR: ν 3561 (OH), 1628 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (d, *J* = 5.3 Hz, 1H), 4.14 (dd, *J* = 5.7, 2.9 Hz, 1H), 3.47 (s, 3H), 3.46 (s, 3 H), 2.83 (d, *J* = 3.2 Hz, 1H), 2.74 (dd, *J* = 17.1, 3.7 Hz, 1H), 2.66 (dd, *J* = 17.1, 8.3 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.7, 106.0, 68.0, 55.8, 55.1, 44.7, 30.8. HRMS calculated for $C_7H_{14}O_4$: 162.0900; found: 185.0794 (M+ + Na, recalculated 185.0790). GC: CP CHIRALSIL DEX CB column (160 ºC, 13.4 Psi), R_t = 3.6 min (minor), R_t = 5.1 min (major).

4.2.13. (*R*)-5-Hydroxy-6,6-dimethoxyhexan-3-one *iso*-12m

Yellow oil (19 mg, 43%); $[\alpha]_D^{26}$ = –20 (*c* 0.5, $CHCl_3$, ee 95% from GC); R_f = 0.25 (Hex/EtOAc: 1/1). IR: ν 3428.1 (OH), 1592.9 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (d, *J* = 5.3 Hz, 1H), 4.19–4.10 (m, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 2.87 (d, *J* = 4.0 Hz, 1H), 2.72 (dd, *J* = 17.0, 4.1 Hz, 1H), 2.63 (dd, *J* = 17.0, 7.9 Hz, 1H), 2.50 (c, *J* = 7.3 Hz, 2H), 1.08 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.4, 106.0, 68.1, 55.7, 55.1, 43.4, 36.9, 7.6. HRMS calculated for $C_8H_{16}O_4$: 176.1049; found: 177.1122 (M^+ + H, calculated 177.1127). GC: CP CHIRALSIL DEX CB column (140 ºC, 13.4 Psi), R_t = 6.9 min (minor), R_t = 7.4 min (major).

4.2.14. (3*S*,4*R*)-4-Hydroxy-3,5,5-trimethoxypentan-2-one 12n

Yellow oil (14 mg, 30%); $[\alpha]_D^{26}$ = –18 (*c* 0.8, $CHCl_3$, *anti/syn:* 91/9, ee_{anti} 90% from GC); R_f = 0.2 (Hex/EtOAc: 1/1). IR: ν 3599 (OH), 1591 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.43 (d, *J* = 6.7 Hz, 1H), 3.98 (dd, *J* = 5.2, 1.5 Hz, 1H), 3.80 (d, *J* = 3.7 Hz, 1H), 3.50 (s, 3H), 3.47 (m, 5H), 3.41 (s, 3H), 2.5 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 103.2, 87.2, 77.2, 60.4, 21.1, 14.2. HRMS calculated for $C_8H_{16}O_5$: 192.0998; found: 215.0888 (M^+ + Na, recalculated 215.0895). GC: LIPODEX-A column (140 ºC, 13.4 Psi), R_t = 10.1 min (minor), R_t = 10.4 min (major).

4.2.15. (3*S*,4*R*)-3-(Benzyloxy)-4-hydroxy-5,5-dimethoxypentan-2-one 12o

Brown oil (33 mg, 49%); $[\alpha]_D^{26}$ = –28 (*c* 1.0, $CHCl_3$, *anti/syn:* 95/5, ee_{anti} 94% from HPLC); R_f = 0.15 (Hex/EtOAc; 1:1). IR: ν 3453 (OH), 1530 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.31 (m, 5H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 6.1 Hz, 1H), 4.01 (d, *J* = 3.1 Hz, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.5, 173.3, 128.5, 128.0, 103.1, 84.7, 73.3, 72.4, 55.5, 54.5, 27.3. HRMS calculated for $C_{14}H_{20}O_5$: 268.131; found: 291.1197 (M^+ + Na, recalculated 291.1208). HPLC: Chiralpak AD-H column (90% hexane, 10% Pr^iOH, 25ºC, 1 mL/min, 210 nm), R_t = 9.5 min (minor), R_t = 11.2 min (major).

4.2.16. (3*S*,4S)-3-Chloro-4-hydroxy-5,5-dimethoxypentan-2-one 12p

Colorless oil (26 mg, 53%); $[\alpha]_D^{26}$ = –26 (*c* 1.1, $CHCl_3$, *anti/syn:* 90/10, ee_{anti} 97% from GC); R_f = 0.21 (Hex/EtOAc; 1:1). IR: ν 3588 (OH), 1541 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.51 (d, *J* = 4.6 Hz, 1H), 4.40 (d, *J* = 5.4 Hz, 1H), 4.12 (m, 1H), 3.51 (s, 3H), 3.46 (s, 3H), 2.83 (d, *J* = 5.8 Hz, 1H), 2.37 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 103.6, 73.3, 62.5, 56.0, 55.6, 27.8. HRMS calculated for $C_7H_{13}ClO_4$: 196.0502; found: 219.0408 (M^+ + Na, recalculated 219.0408). GC: LIPODEX-E column (140 ºC, 13.4 Psi), R_t = 12.5 min (minor), R_t = 13.4 min (major).

4.2.17. (2*S*,3*R*)-2-Benzyl-4,4-dimethoxybutane-1,2-diol 14[4i]

After the aldol reaction took place, the crude product was diluted with MeOH (1 mL) then $NaBH_4$ (38 mg, 1 mmol) was added at 0 ºC and the mixture was stirred for 1 h at rt. The resulting residue was purified by flash chromatography (Hex/EtOAc: 1/1) to yield the *anti/syn* (7/1) diastereomeric mixture, as a colorless oil (38 mg, 64%); R_f = 0.37 (Hex/EtOAc: 1/1). IR: ν 3420, 2933, 1060. ^{1}H NMR (*anti*-product, 400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 5H), 4.44 (d, *J* = 6.8 Hz, 1H), 3.84 (dd, *J* = 8.6, 5.7 Hz, 1H), 3.69 (m, 1H), 3.63 (m, 1H), 3.44 (s, 3H), 3.32 (s, 3H), 2.87 (s, 1H), 2.85 (s, 1H), 2.73 (br s, 1H), 2.60 (br s, 1H), 2.12 – 2.00 (m, 1H). ^{13}C NMR (*anti*-product, 101 MHz, $CDCl_3$) δ 140.1, 129.2, 128.4, 126.1, 105.1, 73.2, 62.4, 55.1, 54.4, 42.1, 35.1. HPLC (*anti*-product): Chiralpak AD-H column (97% hexane, 3% Pr^iOH, 25ºC, 1 mL/min, 210 nm), R_t = 27.6 min (minor), R_t = 31.3 min (major).

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