ARTICLE

Development of an α'-hydroxy enone for the aminocatalytic asymmetric formal conjugate addition of aldehydes to acrylates, vinyl ketones and acrolein ‡†

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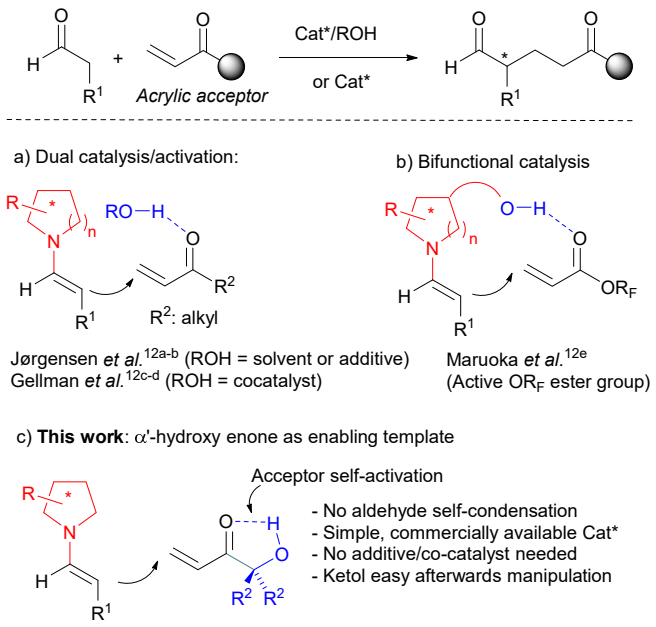
Aminocatalytic asymmetric conjugate addition of aldehydes to Michael acceptors is a well established C-C bond forming methodology. However, various acrylic-type acceptors, including acrylic acid derivatives and acrolein, remain reluctant. Here we demonstrate that the internal H-bonding self-activation in α'-hydroxy enones allows them to react smoothly with enolizable aldehydes using commercially available aminocatalysts to afford adducts in good yields and high enantioselectivity. Straightforward conversion of the ketol moiety of these adducts into aldehyde, ketone and carboxylic acid functionalities offers an indirect, unified entry to products derived from acrolein, alkyl-vinyl ketones and acrylates, respectively.

Introduction

Catalytic enantioselective conjugate additions are one of the most popular carbon-carbon bond-forming reactions in organic synthesis.[1] A large number of organocatalytic variants have been developed to date.[2,3] In this context, amine catalysed Michael addition reactions of aldehydes, via enamine intermediate, to a variety of active acceptors including nitroolefins,[4] alkylidenemalonates,[5] bis(sulfonyl) ethylenes,[6] vinyl phosphonates,[7] enals,[8] 4-oxo-2-enoates, 2-ene-1,4-diones,[9] maleimides,[10] and α,β-unsaturated thiol esters[11] have been reported. In contrast, the addition of common acrylic systems, (including acrylates, acrylamides, vinyl ketones and acrolein), has been much less developed (Scheme 1).[12] To achieve these transformations chemoselectively, the cross-addition process needs to override the inherent tendency of aldehydes for self-condensation. Under usual aminocatalytic conditions, it is difficult to fulfill this requirement as the reaction of the transient enamines with simple acrylic systems is unpractical at low temperatures, while at higher temperatures undesired aldehyde self-condensation takes place preferentially. In order to overcome these difficulties a few approaches to enhance the electrophilicity of the acrylic reagent by hydrogen bonding using either a cocatalyst[12a-d] or a catalyst incorporating a H-bond donor[12e] were reported (Scheme 1a,b). Even so, the highly enantioselective addition reaction of aldehydes to alkyl vinyl ketones with chains larger than methyl/ethyl has not been well established yet, while the addition to acrolein is still pending because the resulting reaction product is another enolizable aldehyde. Herein we describe a unified approach to the aminocatalytic asymmetric Michael addition of aldehydes to formally various acrylic systems based on the use of α'-hydroxy enones as self-activated



Scheme 1. Aminocatalytic strategies for the enantioselective Michael addition of aldehydes to vinyl ketones and acrylates.

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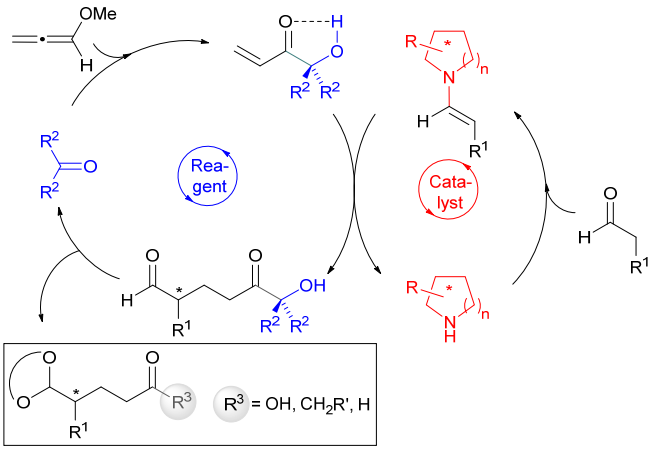
Michael acceptors and the versatility of the ketol moiety as precursor of aldehyde, ketone and carboxylic acid functionalities (Scheme 1c).

Results and discussion

Background and working hypothesis. Prior work from these laboratories has documented α'-hydroxy enones to be very useful Michael acceptors in asymmetric catalysis with either metallic catalysts[13] or chiral organobases.[14] These studies revealed that the ability of α'-hydroxy enones for two-point catalyst coordination and the high preference for the enone to adopt an *s-cis* conformation in these substrates because of steric constraints, are key. In this context, we wondered if the internal COH·····O=C H-bonding, a known self-activation feature of α'-hydroxy enones,[15] would make these acceptors more reactive than aldehydes for attaining threshold chemoselectivity. Given the ease with which the ketol moiety of the resulting adducts could be converted into carboxy, ketone or aldehyde functionalities, the approach would provide a unified and practical solution to the above limitations. In this conception, it is important to note that there is not carbon waste formation as the $(R^2)_2C=O$ ketone unit released during ketol elaboration would reenter the reagent cycle upon coupling with methoxyallene, which is available in bulk (Scheme 2).

Template screening and reaction optimization. Considering that α'-hydroxy enone **2A** (4-benzyl-4-hydroxy-5-phenylpent-1-en-3-one), easily prepared from methoxyallene and 1,3-diphenylacetone, led to high enantioselectivities in conjugate addition reactions using chiral Brønsted bases as catalysts,[16] we began our study exploring the reaction with hydrocinnamaldehyde **1a** in the presence of 20 mol% of Jørgensen-Hayashi catalyst **C1**[4e,4j,17]. This catalyst has been amply used in a wide variety of organocatalytic reactions and is commercially available and/or easy to prepare. The reaction



Scheme 2. Proposal for the formal conjugate addition of aldehydes to acrylates, vinyl ketones and acrolein based on the development of an α'-hydroxy enone as Michael acceptor.

was carried out without added solvent[18] and, for reasons that will be outlined later, the resulting aldehyde product was isolated as their acetal upon one-pot addition of 1,2-ethanediol and *p*- toluensulfonic acid as catalyst. Full conversion was reached after 44 h, and product **3Aa** of 78:22 enantiomeric ratio (*er*) was isolated (Table 1, entry 1). Importantly, self-aldolization products were not detected by ^{1}H NMR. Attempts to further increase the enantioselectivity by diminishing the reaction temperature to 0/5 °C were futile for this catalyst because the reaction became too slow.

Subsequently, and in order to determine whether the nature of the geminal R^2 substituents has any significant influence on the enantioselectivity and on the rate of de conjugate addition, we tested the reaction using a less sterically hindered α'-hydroxy enone. So, 4-hydroxy-4-methylpent-1-en-3-one **2B**,[14] was submitted to react with hydrocinnamaldehyde **1a** in presence of **C1** under the optimized conditions (neat reaction mixture, catalyst 20 mol%). In this case, the reaction was complete in 16 h and a higher enantiopurity (97:3 *er*) was obtained (entry 2).

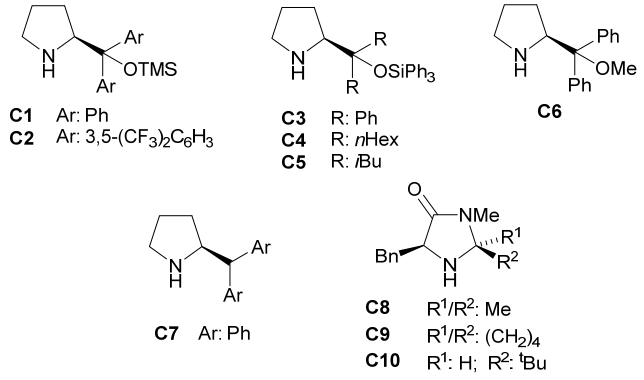
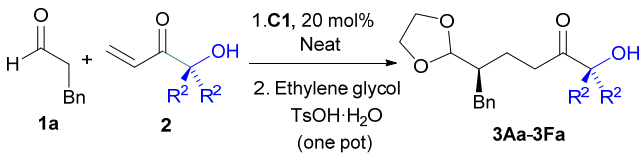


Figure 1. Aminocatalysts screened within this work.

Table 1. C1-catalyzed reaction of hydrocinnamaldehyde with various α'-hydroxy enones **2A-F**.[a]



Entry	R^2	Enone	t (h)	*er*[b]	Conv. (%)[c]
1	Bn	**2A**	44	78:22	>99
2	Me	**2B**	16	97:3	>99
3	Pr	**2C**	29	88:12	>99
4	*i*Bu	**2D**	45	89:11	91
5	-$(CH_2)_5$-	**2E**	14	89:11	>99
6	Ph	**2F**	15	87:13	81

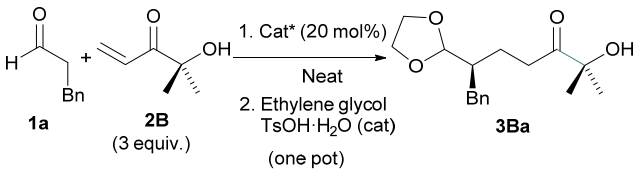
[a]Reactions run at RT and 0.5 mmol scale. Ratio of **1a**:**2**:**C1** 1:3:0.2. [b]Determined by chiral HPLC analysis of products **3Aa–3Fa**. [c]Determined by ^{1}H NMR.

Due to the great difference in the observed results in terms of both reactivity and stereoselectivity in the conjugate addition reaction of hydrocinnamaldehyde **1a** by the use of α'-hydroxy enones **2A** or **2B**, we wanted to explore other enones with alkyl chains longer than methyl R^2= nPr (**2C**) (entry 3), bearing a branched alkyl chain R^2= *i*Bu (**2D**) (entry 4) or a cycloalkyl group **2E** (entry 5). However, enones **2C** and **2D** were comparatively less reactive templates than **2B**, and did not lead to any improvement on enantioselectivity either. The cyclohexyl enone **2E** resulted the most reactive along with **2B**, but led to slightly diminished enantioselectivity (89:11 *er*) (entry 5). Finally, we prepared an α´-hydroxy enone with phenyl groups attached at Cα´, **2F**. Nevertheless, with this *gem*-diphenyl enone, again, neither reactivity nor selectivity was improved (81% conversion after 15 h, 87:13 *er*) (entry 6). From this short screening, it could be inferred that the reactivity of enones **2** under the present conditions is quite sensitive to steric variations at Cα'. However, there is not clear correlation between the nature of the R^2 substituents on the α'-hydroxy enones and the reaction enantioselectivity, perhaps because in some cases product racemization may occur via reversible enamine formation (*vide infra*).

With **2B** selected as optimum enone template, we set to investigate the influence of other catalysts on the stereoselectivity of the hydrocinnamaldehyde addition reaction (Figure 1).

As the results in Table 2 show, the reaction in the presence of 20 mol% of catalyst **C2** was extremely slow, with only 10% conversion after 89 hours at room temperature (entry 3). The

Table 2. Catalyst screening for the addition reaction of hydrocinnamaldehyde **1a** to **2B**.[a]



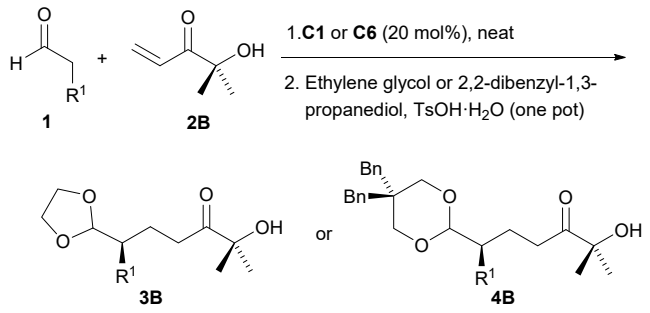
Entry	Catalyst	t (h)	*er*[b]	Conv. (%)[c]
1	**C1**	**16**	**97:3**	**>99**
2[d]	**C1**	15	97:3	71
3	**C2**	89	--	10
4	**C3**	64	90:10	>99
5	**C4**	163	--	41
6	**C5**	64	77:23	>99
7	**C6**	**16**	**95:5**	**>99**
8	**C7**	87	68:32	>99
9	**C8**	24	94:6	81
10	**C9**	111	92:8	83
11	**C10**	15	--	0

[a]Reactions run at RT and 0.5 mmol scale with a mol ratio of **1a**:**2B**:catalyst 1:3:0.2. [b]*Er* of product **3Ba** determined by chiral HPLC analysis. [c]Determined by ^{1}H NMR. [d]Using 2 equiv of **2B**.

O-Me analog **C6**[12c] (Gellman catalyst, entry 7) was as active as **C1**, affording full conversion within the 16 h to provide a product with slightly inferior enantiopurity (95:5 *er*). Catalyst **C3** (entry 4), with a bulkier *O*-$SiPh_3$ ether group was comparatively less active and slightly less selective than **C1**. Similarly, the related *O*-silyl prolinols **C4** and **C5**, which bear two *gem*-dialkyl groups resulted inferior in terms of both activity and selectivity (entries 5, 6). (Diphenylmethyl)pyrrolidine **C7**, which is deprived of the silyl ether group, was also less selective than prolinol ether derivatives (68:32 *er*) (entry 8). Then imidazolidinone catalysts were evaluated. Catalysts **C8**[19] and **C9**[12d] were highly selective, with product of 94:6 and 92:8 *er* respectively, being obtained, but the reaction required long reaction times for completion in both cases (entries 9, 10). In addition, with these latter catalysts about 5-10% of self-aldolization product was obtained. In its turn, imidazolidinone **C10** resulted totally ineffective (entry 11). Finally, entry 2, reducing the excess amount of **2B** with respect to aldehyde **1a** from 3 to 2 equivalents slowed the reaction considerably.

Reaction scope and product derivatization. With **2B** selected as enone template, and **C1** and **C6**, both commercially available, selected as the optimum catalysts, the generality of the method for other enolizable aldehydes was explored (Table 3). The reaction products were isolated as the respective ethane-1,2-diol or 2,2-dibenzyl-1,3-propanediol monoacetals which facilitates the determination of enantioselectivity by HPLC analysis while, at the same time, discriminates both carbonyl units for further chemical elaboration. For example,addition reaction of propionaldehyde **1b** to 3 eq. of α'-hydroxy enone **2B** at room temperature for 4 h in presence of **C1**, provided the aldehyde product isolated as acetal **4Bb** in 78% yield and 89:11 enantiomeric ratio (entry 3). Longer reaction times caused progressive erosion of the *er* very likely due to product epimerization via enamine formation. Thus, when the reaction of entry 3 was allowed to stir for 20 h at room temperature, the enantiomeric ratio diminished to 83:17. With this aldehyde the enantioselectivity could be improved by lowering the temperature. Thus, the reaction could be carried out at 5 ºC for 40 h giving rise the desired adduct as a 92:8 mixture of enantiomers (entry 4). Under these conditions no self-aldolization products of propionaldehyde were detected by ^{1}H NMR. Other aldehydes with linear or branched chain structures such as isovaleraldehyde **1c**, hexanal **1d**, and 3-cyclohexylpropionaldehyde **1e**, were also added to hydroxy enone **2B** to produce the corresponding adducts **4** with high enantiomeric ratios and good yields (entries 6, 8, 10). Aldehydes bearing chain unsaturation (4-pentenal **1f**, 4-pentynal **1h**) or ether and halide functional groups (4-benzyloxybutanal **1g**, 5-bromopentanal **1i**) were also well tolerated affording the corresponding addition adducts satisfactorily (entries 12, 15 and 14, 16). With these aldehydes, the use of lower temperatures did not increase the enantioselectivity. On the other hand, pyrrolidine **C6**, the *O*-Me analog of **C1**, was also a competent catalyst capable of promoting the above addition reactions with similar efficiency but slightly lower enantioselectivity (entries 2, 5, 7, 9, 11 and 13).

Table 3. Conjugate addition of aldehydes **1** to hydroxy enone **2B** in the presence of catalyst **C1** or **C6**.[a]



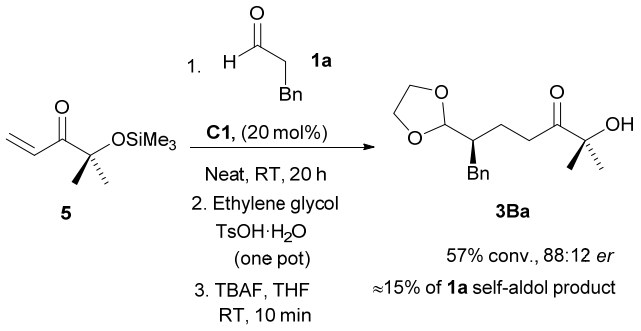
Entry	R^1	Cat	Product	t (h)	*er*[b]	Yield (%)[c]
1	Bn	**C1**	**3Ba**	16	97:3	80
2	Bn	**C6**	**3Ba**	16	95:5	79
3	Me	**C1**	**4Bb**	4	89:11	78
4[d]	Me	**C1**	**4Bb**	40	92:8	75
5	Me	**C6**	**4Bb**	4	85:15	70
6	$(Me)_2CH$	**C1**	**4Bc**	48	94:6	73
7	$(Me)_2CH$	**C6**	**4Bc**	20	95:5	75
8	$CH_3(CH_2)_3$	**C1**	**4Bd**	19	95:5	70
9	$CH_3(CH_2)_3$	**C6**	**4Bd**	19	92:8	70
10	$cHexCH_2$	**C1**	**4Be**	24	95:5	81
11	$cHexCH_2$	**C6**	**4Be**	24	91:9	76
12	$CH_2=CHCH_2$	**C1**	**4Bf**	24	95:5	75
13	$CH_2=CHCH_2$	**C6**	**4Bf**	24	91:9	73
14	$BnO(CH_2)_2$	**C1**	**3Bg**	15	94:6	75
15	$CH{\equiv}CCH_2$	**C1**	**4Bh**	15	96:4	78
16	$Br(CH_2)_3$	**C1**	**4Bi**	15	93:7	82

[a]Reactions run at RT and 0.5 mmol scale. Ratio of **1**:**2B**:catalyst 1:3:0.2. [b]Determined by chiral HPLC analysis. [c]Yield of isolated product after column chromatography. [d]Reaction was carried out at 5 °C.

However, attempts to extrapolate the present catalytic approach to enones bearing an alkyl or aryl substituent at the enone α- or β-position were unsuccessful so far.[20]

In order to assess the importance of the hydroxyl group of the enone template in the above reactions, we prepared the *O*-trimethylsilyl-protected enone **5** by silylation of **2B** with 3-(trimethylsilyl)-2-oxazolidinone. Reaction of **5** with hydrocinnamaldehyde in the presence of 20 mol% of **C1** at room temperature for 20 hours and subsequent acetalization and desilylation of the addition adduct, led to the product **3Ba** in 57% conversion and a 88:12 *er* (Scheme 3). In addition, formation of about 15% of aldehyde self-aldolization was observed. This assay was indicative of the key role played by the hydroxyl group of enones **2** in activating them as Michael acceptors via intramolecular H-bonding.

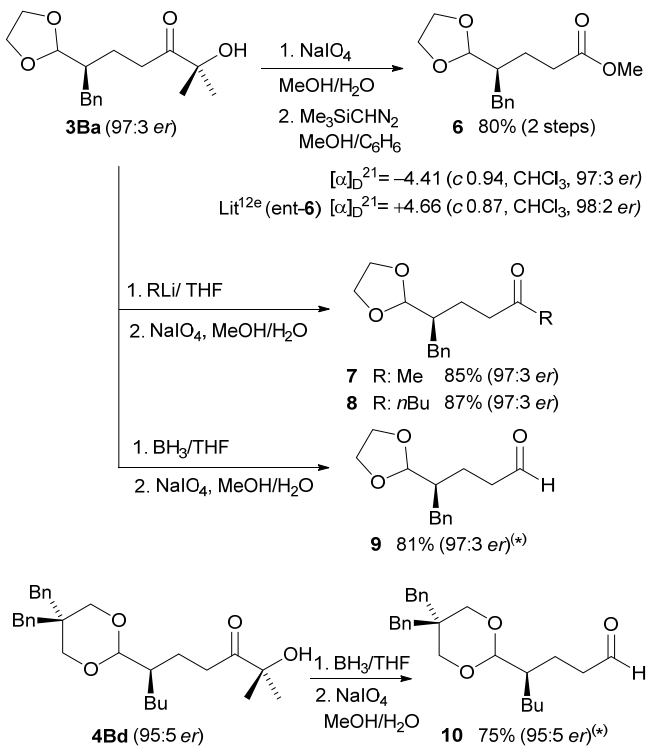
To illustrate the versatility of the method for further synthetic perusal, the ketol moiety in adduct **3Ba** was subjected to various transformations (Scheme 4). For instance, oxidative cleavage of **3Ba** with sodium metaperiodate in methanol at room temperature furnished the corresponding carboxylic acid



Scheme 3. Control experiment with silyl-protected **5**.

which was treated with (trimethylsilyl)diazomethane to afford methyl ester **6** in 80% yield over the two steps. Comparison of the optical rotation of thus obtained material with literature value[12e] served to establish the configuration of products and hence the stereochemical course of the catalytic reactions. Alternatively, the addition of methyllithium to **3Ba** carbonyl group, followed by treatment with $NaIO_4$, provided ketone **7** in 85% yield. Similarly, the addition of *n*-butyllithium to **3Ba** and subsequent diol cleavage provided a practical entry to ketone **8** in 87% yield over the two steps, product that can not be efficiently produced by direct addition to the corresponding butyl vinyl ketone.

On the other hand, vinyl ketone **2B** may also act as acrolein equivalent in the above catalytic reactions, enabling short and quick access to 1,5-dialdehyde products or derivatives therefrom that are



Scheme 4. Elaboration of adducts. (*) *Er* determined after reduction to the corresponding alcohols **9'** and **10'**.

otherwise difficult to produce. For example, reduction of **3Ba** with BH_3 and subsequent oxidative diol cleavage led to aldehyde **9** in 81% overall yield. Similarly, adduct **4Bd** could be converted into aldehyde **10** in 75% yield. Overall, the latter two examples represent processes in which perfect differentiation among two discrete aldehyde functionalities participating in asymmetric carbon-carbon bond formation is achieved. In all the above elaborations of adducts acetone is the only organic byproduct formed, another aspect of practical interest in terms of product isolation.[21] The enantiopurity of the ester and ketone products **6**, **7** and **8** was determined to be identical (97:3 *er*) to that of the starting sample **3Ba**. In the case of aldehyde products **9** and **10**, preservation of the enantiopurity was determined after reduction with $NaBH_4$/MeOH to the respective alcohol derivatives **9'** and **10'**.

On the basis of the observed stereochemistry, a plausible transition state model can be proposed as shown in Figure 2.

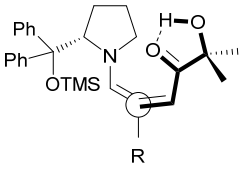


Figure 2. A plausible transition-state model for the key C-C bond formation in the above catalytic reactions.

In accordance with previous studies,[12b] the activated enone, probably adopting its most stable *s-cis* conformation, approaches the available *Si* face of the *E*-enamine. The selectivity of the organocatalytic addition could be explained by an acyclic synclinal transition state based on Seebach's model[22] in which there could be favourable electrostatic interactions between the nitrogen of the enamine and the carbonyl moiety. The bulky *tert*-alkyl group attached to pyrrolidine would induce the *E*-enamine to adopt an *s-trans* conformation with its *Re*-face sterically shielded.

Conclusions

In summary, we have documented a practical and convenient enone template which reacts with simple enolizable aldehydes smoothly and chemoselectively in the presence of commercially available prolinol ether aminocatalysts to afford the corresponding Michael adducts in high yield and enantioselectivity. Significantly, formation of aldehydes self-condensation sideproducts under these conditions is marginal. Given that conversion of the ketol moiety of thus obtained adducts into ester, alkyl-ketone and carbaldehyde functions is straightforward, and the ease with which α'-hydroxy enones may be prepared in large scale from ketones and methoxyallene, this method represents a unified and practical solution to the formal crossed conjugate addition of enolizable aldehydes to acrylic esters, vinyl alkyl ketones and acrolein evenly.

Experimental

General Information

^{1}H NMR spectra were recorded on a Bruker Ascend 400 (400 MHz) spectrometer and data were reported as follow: chemical shifts in ppm from tetramethylsilane (TMS) or relative to residual $CHCl_3$ δH (7.26 ppm) as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, dd = double-doublet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were measured on a Bruker Ascend 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent $CHCl_3$ δC (77.00 ppm) as an internal standard. Analytical high performance liquid chromatography (HPLC) was performed on a Jasco MD2010 instruments equipped with photodiode array UV detector and CD detector, using Daicel Chiralpak AD-3, IC-3, AY-3, Chiralcel OD-H, Phenomenex Lux Amylose-1 and Cellulose-1, 4.6 mm x 25 cm columns. Optical rotations were recorded on a Jasco P-2000 polarimeter. MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model) on a UPLC-DAD-QTOF, UHPLC-Mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector, Waters Sunapt G2 or on an Agilent Thermoquest LCT spectrometer. Melting points were determined in a Mettler melting point apparatus and microscope and were uncorrected. Purification of reaction products was carried out by flash chromatography using silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60F PF254 plates.

All solvents were of p.a. quality and were dried by standard procedures prior to use if necessary. Unless otherwise specified, materials were obtained from commercial sources and used without purification. The commercially available aldehydes were distilled and stored under nitrogen atmosphere at -17 °C. 3-Cyclohexylpropanal,[23] 4-benzyloxybutanal,[24] pent-4-ynal[25] and 5-bromopentanal[26] were synthesized according to literature procedure and used after purification by column chromatography.

Catalysts **C1**, **C2**, **C6**, **C7**, **C8** and **C10** were purchased from Sigma-Aldrich. Catalysts **C3**,[27] **C4**,[28] **C5**[29] and **C9**[12d] were prepared according to the procedures described previously in literature.

Preparation of α'-hydroxy enones (2). General procedure

To a solution of methoxypropadiene (3.50 g, 50 mmol) in dry Et_2O (100 mL) at -40 °C, nBuLi (2.5 M in hexanes, 22 mL, 55 mmol) was added under nitrogen and the reaction was stirred at -40 °C for 10 min. The corresponding ketone (55 mmol) in dry Et_2O (55 mL) was added within 5 min. The reaction was stirred at the same temperature for 0.5 h and quenched with H_2O (100 mL). The resulting mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford the corresponding addition product that was employed in the next step without further purification.

This compound was added dropwise to 5% aq H_2SO_4 (110 mL) at 0 °C and the mixture was stirred for 1.5 h. After this time, the reaction was allowed to warm to room temperature and the solution was saturated with solid NaCl. The mixture was

extracted with Et_2O (5 x 60 mL) and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed to give a yellow oil which upon purification afforded the enone.

4-Benzyl-4-hydroxy-5-phenylpent-1-en-3-one (2A)

The enone **2A** was prepared according to general procedure from commercially available 1,3-diphenyl-2-propanone (11.56 g, 55 mmol). Upon purification by silica gel column chromatography (ethyl acetate: hexane = 1:20) the title enone was obtained as a white solid. Yield: 9.72 g, 73%. m.p.: 91-93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.21 (m, 10H), 6.99 (dd, *J* = 16.8 Hz, *J* =10.4 Hz, 1H), 6.41 (dd, *J* = 16.8 Hz, *J* =1.6 Hz, 1H), 5.85 (dd, *J* = 10.4 Hz, *J* = 1.6 Hz, 1H), 3.71 (s, 1H), 3.22 (d, *J* = 13.8 Hz, 2H), 3.13 (d, *J* = 13.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.8, 135.3, 130.9, 130.3, 129.9, 128.1, 126.9 , 81.7, 44.3. All spectroscopic data were consistent with those previously reported.[16]

4-Hydroxy-4-methylpent-1-en-3-one (2B)

The enone **2B** was prepared according to general procedure using acetone (4.04 mL, 55 mmol). Upon distillation the title enone was obtained as a colorless liquid. Yield: 5.02 g, 88%. b.p. 45 °C (13 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.76 (dd, *J* = 17.2 Hz, *J* =10.4 Hz, 1H), 6.55 (dd, *J* = 17.2 Hz, *J* =2.0 Hz, 1H), 5.87 (dd, *J* = 10.4 Hz, *J* = 2.0 Hz, 1H), 3.88 (s, 1H), 1.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.5, 131.0, 128.9, 75.4, 26.1. All spectroscopic data were consistent with those previously reported.[16]

4-Hydroxy-4-propylhept-1-en-3-one (2C)

The enone **2C** was prepared according to general procedure from commercially available heptan-4-one (6.28 g, 55 mmol). Upon purification by silica gel column chromatography (ethyl acetate: hexane = 1:20) the title enone was obtained as a colorless liquid. Yield: 6.30 g, 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.71 (dd, *J* = 17.0 Hz, *J* =10.3 Hz, 1H), 6.51 (dd, *J* = 17.0 Hz, *J* =1.8 Hz, 1H), 5.80 (dd, *J* = 10.3 Hz, *J* = 1.8 Hz, 1H), 3.92 (s, 1H), 1.77 – 1.59 (m, 4H), 1.50 – 1.32 (m, 2H), 1.05 – 0.91 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.7, 130.7, 129.1, 80.9, 40.7, 16.5, 14.3. MS (ESI, *m*/*z*): calcd for $C_{17}H_{25}O_4$ (M, H^+), 171.1385; found, 171.1379.

4-Hydroxy-4-isobutyl-6-methylhept-1-en-3-one (2D)

The enone **2D** was prepared according to general procedure from commercially available 2,6-dimethylheptan-4-one (7.82 g, 55 mmol). Upon purification by silica gel column chromatography (ethyl acetate: hexane = 1:20) the title enone was obtained as a colorless liquid. Yield: 7.73 g, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.73 (dd, *J* = 17.0 Hz, *J* =10.3 Hz, 1H), 6.51 (dd, *J* = 17.0 Hz, *J* =1.8 Hz, 1H), 5.79 (dd, *J* = 10.3 Hz, *J* = 1.8 Hz, 1H), 3.96 (s, 1H), 1.69 – 1.55 (m, 6H), 0.90 (d, *J* = 6.4 Hz, 6H),), 0.75 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.4, 130.2, 129.8, 81.4, 47.9, 24.3, 24.1, 23.9. MS (ESI, *m*/*z*): calcd for $C_{17}H_{25}O_4$ (M, H^+), 199.1698; found, 199.1692.

1-(1-Hydroxycyclohexyl)prop-2-en-1-one (2E)

The enone **2E** was prepared according to general procedure from cyclohexanone (5.40 g, 55 mmol). Upon purification by silica gel column chromatography (ethyl acetate: hexane = 1:20) the title enone was obtained as a colorless oil. Yield: 6.29 g, 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.83 (dd, *J* = 16.8 Hz, *J* =10.4 Hz, 1H), 6.47 (d, *J* = 16.8 Hz, 1H), 5.79 (d, *J* = 10.4 Hz, 1H), 1.75 – 1.24 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.7, 130.6, 129.2, 77.1, 33.3, 25.2, 21.0. All spectroscopic data were consistent with those previously reported.[30]

1-Hydroxy-1,1-diphenylbut-3-en-2-one (2F)

The enone **2F** was prepared according to general procedure from commercially available benzophenone (10.02 g, 55 mmol). Upon purification by silica gel column chromatography (ethyl acetate: hexane = 1:20) the title enone was obtained as a yellowish oil. Yield: 7.86 g, 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.32 (m, 10H), 6.71 (dd, *J* = 17.0 Hz, *J* =10.3 Hz, 1H), 6.53 (dd, *J* = 17.0 Hz, *J* =1.8 Hz, 1H), 5.74 (dd, *J* = 10.3 Hz, *J* = 1.8 Hz, 1H), 5.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.3, 141.1, 131.0, 130.6, 128.5, 128.3, 128.2, 84.6. MS (ESI, *m*/*z*): calcd for $C_{17}H_{25}O_4$ (M, H^+), 239.1072; found, 239.1076.

4-Methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (5)

3-(Trimethylsilyl)-2-oxazolidinone (TMSO) (1.5 equiv., 3.4 mL, 22.5 mmol) and 3 drops of trifluoromethanesulfonic acid were added to enone **2B** (1 equiv., 1.68 g, 15 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with pentane (20 mL), the solid was filtered and the organic solution was washed with water (20 mL) and $NaHCO_3$ sat. sol. (20 mL), dried with $MgSO_4$ and concentred under reduced pressure to afford the title compound (**5**) as colorless oil. Yield: 2.6 g, 93%. ^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.03 (dd, *J* = 17.3 Hz, *J* = 10.4 Hz, 1H), 6.38 (dd, *J* = 17.3 Hz, *J* = 2.1 Hz, 1H), 5.72 (dd, *J* = 10.4 Hz, *J* = 2.1 Hz, 1H), 1.37 (s, 6H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.4, 130.4, 128.8, 79.0, 26.9, 1.8. All spectroscopic data were consistent with those previously reported.[16]

General procedure for conjugate addition of aldehydes to α'-hydroxy enones and acetalization

The corresponding aldehyde (0.5 mmol) was added to a mixture of α'-hydroxy enone (1.5 mmol) and catalyst (0.1 mmol). The resulting reaction mixture was stirred at room temperature for the time specified in Tables. Subsequently, the reaction mixture was diluted with CH_2Cl_2 (2,5 mL) and 1,2-ethanediol (155 mg, 2.5 mmol) or 2,2-dibenzyl-1,3-propanediol (641 mg, 2.5 mmol) and *p*-toluensulfonic acid monohydrate (48 mg, 0.25 mmol) were added. After stirring for 12 h dichloromethane (5 mL) was added and the reaction was quenched by addition of water. The organic layer was washed with saturated solution of $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated in vacuo after filtration. Purification by silica gel column chromatography (ethyl acetate: hexane = 1:9) gave the corresponding acetalized product.

The racemic samples required for analytical (HPLC) purposes were obtained by running the reactions in the presence of equimolar amounts of the *R*- and *S*-configured commercially available Hayashi catalysts.

(*S*)-2-Benzyl-6-(1,3-dioxolan-2-yl)-2-hydroxy-1,7-diphenylheptan-3-one (3Aa)

The title compound was obtained starting from hydrocinnamaldehyde **1a** (67.1 mg, 0.5 mmol), α'-hydroxy enone **2A** (399.5 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 173 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 – 7.13 (m, 15H), 4.68 (d, *J*=3.6 Hz, 1H), 3.91 – 3.89 (m, 2H), 3.86 – 3.82 (m, 2H), 3.33 (s, 1H), 3.07 (d, *J*=13.6 Hz, 2H), 2.96 (dd, *J*=13.6 Hz, *J*=5.0 Hz, 2H), 2.83 (dd, *J*=13.8 Hz, *J*=5.8 Hz, 1H), 2.50 – 2.33 (m, 3H), 1.96 – 1.88 (m, 1H), 1.62 – 1.52 (m, 1H), 1.44 – 1.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 213.5, 140.2, 135.7, 135.6, 130.1, 129.2, 128.4, 128.3, 126.9, 126.1, 106.0, 82.5, 65.0, 64.9, 44.8, 44.7, 42.5, 36.3, 35.9,

22.0. MS (ESI, *m*/*z*): calcd for $C_{29}H_{33}O_4$ (M, H^+), 445.2379; found, 445.2386.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel AY-3, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 29.1 min (minor) and 37.6 min (major)).

(*S*)-6-(1,3-Dioxolan-2-yl)-2-hydroxy-2-methyl-7-phenylheptan-3-one (3Ba)

The title compound was obtained starting from hydrocinnamaldehyde **1a** (67.1 mg, 0.5 mmol), α'-hydroxy enone **2B** (171.2 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 117 mg, 80%. $[\alpha]_D^{20} = -10.7°$ (*c*=1.25, 97:3 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.20 (m, 5H), 4.77 (d, *J*=3.6 Hz, 1H), 4.01 – 3.95 (m, 2H), 3.89 – 3.83 (m, 2H), 3.77 (s, 1H), 2.92 (dd, *J*=13.8 Hz, *J*=5.6 Hz, 1H), 2.63 – 2.47 (m, 3H), 2.04 – 1.98 (m, 1H), 1.86 – 1.77 (m, 1H), 1.70 – 1.61 (m, 1H), 1.30 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.3, 140.1, 129.2, 128.4, 126.1, 106.0, 76.1, 65.0, 64.9, 42.7, 36.2, 33.6, 26.6, 26.5, 22.8. MS (ESI, *m*/*z*): calcd for $C_{17}H_{25}O_4$ (M, H^+), 293.1753; found, 293.1760.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 23.4 min (major) and 37.9 min (minor)).

(*S*)-2-(1,3-Dioxolan-2-yl)-6-hydroxy-1-phenyl-6-propylnonan-5-one (3Ca)

The title compound was obtained starting from hydrocinnamaldehyde **1a** (67.1 mg, 0.5 mmol), α'-hydroxy enone **2C** (255.4 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 143 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.20 (m, 5H), 4.79 (d, *J*=3.6 Hz, 1H), 3.98 – 3.93 (m, 2H), 3.92 – 3.84 (m, 3H), 2.93 (dd, *J*=13.7 Hz, *J*=5.6 Hz, 1H), 2.56 (dd, *J*=13.7 Hz, *J*=9.0 Hz, 1H), 2.52 – 2.35 (m, 2H), 2.07 – 2.00 (m, 1H), 1.84 – 1.75 (m, 1H), 1.69 – 1.49 (m, 5H), 1.42 – 1.33 (m, 2H), 0.93 – 0.84 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.4, 140.0, 129.1, 128.4, 126.1, 106.0, 81.5, 65.1, 65.0, 42.6, 41.3, 41.2, 36.2, 34.1, 22.6, 16.6, 16.5, 14.4. MS (ESI, *m*/*z*): calcd for $C_{21}H_{33}O_4$ (M, H^+), 349.2379; found, 349.2375.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 17.6 min (major) and 31.2 min (minor)).

(*S*)-2-(1,3-Dioxolan-2-yl)-6-hydroxy-6-isobutyl-8-methyl-1-phenylnonan-5-one (3Da)

The title compound was obtained starting from hydrocinnamaldehyde **1a** (67.1 mg, 0.5 mmol), α'-hydroxy enone **2D** (297.4 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 130 mg, 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.20 (m, 5H), 4.79 (d, *J*=3.6 Hz, 1H), 4.03 – 3.95 (m, 2H), 3.93 – 3.84 (m, 3H), 2.93 (dd, *J*=13.8 Hz, *J*=5.8 Hz, 1H), 2.60 – 2.42 (m, 3H), 2.09 – 2.02 (m, 1H), 1.87 – 1.78 (m, 1H), 1.69 – 1.45 (m, 7H), 0.92 (d, *J*=5.2 Hz, 3H), 0.91 (d, *J*=5.2 Hz, 3H), 0.78 (d, *J*=6.4 Hz, 3H), 0.73 (d, *J*=6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 215.2, 140.0, 129.1, 128.4, 126.1, 106.0, 82.2, 65.1, 65.0, 48.3, 48.2, 42.7, 36.1, 34.7, 24.3, 24.3, 24.2, 24.2, 24.1, 24.0, 22.5. MS (ESI, *m*/*z*): calcd for $C_{23}H_{37}O_4$ (M, H^+), 377.2692; found, 377.2693.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 17.0 min (major) and 24.9 min (minor)).

(*S*)-4-(1,3-Dioxolan-2-yl)-1-(1-hydroxycyclohexyl)-5-phenylpentan-1-one (3Ea)

The title compound was obtained starting from hydrocinnamaldehyde **1a** (67.1 mg, 0.5 mmol), α'-hydroxy enone **2E** (231.3 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 135 mg, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.20 (m, 5H), 4.78 (d, *J*=3.6 Hz, 1H), 4.02 – 3.96 (m, 2H), 3.92 – 3.84 (m, 2H), 3.56 (s, 1H), 2.91 (dd, *J*=13.8 Hz, *J*=5.8 Hz, 1H), 2.61 – 2.49 (m, 3H), 2.05 – 1.98 (m, 1H), 1.85 – 1.54 (m, 9H), 1.41 – 1.38 (m, 2H), 1.30 – 1.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.6, 140.2, 129.2, 128.4, 126.1, 106.0, 77.9, 65.1, 65.0, 42.7, 36.1, 33.9, 33.8, 25.3, 22.8, 21.1. MS (ESI, *m*/*z*): calcd for $C_{20}H_{29}O_4$ (M, H^+), 333.2066; found, 333.2063.

The enantiomeric ratio was determined by HPLC analysis (Chiralpak AD-3, hexane/isopropanol 95/05, flow rate= 0.5 mL/min, retention times: 38.2 min (major) and 42.6 min (minor)).

(*S*)-5-(1,3-Dioxolan-2-yl)-1-hydroxy-1,1,6-triphenylhexan-2-one (3Fa)

The title compound was obtained starting from hydrocinnamaldehyde **1a** (67.1 mg, 0.5 mmol), α'-hydroxy enone **2F** (357.4 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 135mg, 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.08 (m, 15H), 4.85 (s, 1H), 4.67 (d, *J*=3.2 Hz, 1H), 3.92 – 3.86 (m, 2H), 3.83 – 3.77 (m, 2H), 2.80 (dd, *J*=14.0 Hz, *J*=5.8 Hz, 1H), 2.66 - 2.50 (m, 2H), 2.43 (dd, *J*=14.0 Hz, *J*=8.8 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.78 – 1.69 (m, 1H), 1.59 – 1.50 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.1, 141.6, 140.0, 129.1, 128.4, 128.4, 128.3, 128.1, 128.1, 128.0, 126.0, 105.7, 85.5, 65.0, 64.9, 42.5, 36.5, 35.9, 23.3. MS (ESI, *m*/*z*): calcd for $C_{27}H_{29}O_4$ (M, H^+), 417.2066; found, 417.2060.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 35.8 min (major) and 50.6 min (minor)).

(*R*)-6-(5,5-Dibenzyl-1,3-dioxan-2-yl)-2-hydroxy-2-methylheptan-3-one (4Bb)

The title compound was obtained as a colorless oil, starting from propionaldehyde **1b** (29 mg, 0.5 mmol), α'-hydroxy enone **2B** (171.2 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) and the reaction was carried out at 5 °C. Yield: 154 mg, 75%. $[\alpha]_D^{27} = -0.83°$ (*c*=1.0, 92:8 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.23 (m, 8H), 7.04 – 70.02 (m, 2H), 4.20 (d, *J*=4.0 Hz, 1H), 3.84 (s,1H), 3.75 (d, *J*=11.0 Hz, 2H), 3.52 (d, *J*=11.0 Hz, 2H), 3.07 (d, *J*=13.4 Hz, 1H), 3.03 (d, *J*=13.4 Hz, 1H), 2.73 – 2.59 (m, 2H), 2.47 (s, 2H), 1.98 – 1.89 (m, 1H), 1.78 – 1.72 (m, 1H), 1.64 – 1.56 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.03 (d, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.5, 137.9, 136.3, 131.1, 130.4, 128.2, 128.1, 126.5, 126.3, 104.7, 76.2, 72.7, 72.6, 39.6, 39.3, 37.1, 37.0, 33.4, 26.6, 26.5, 25.5, 14.3. MS (ESI, *m*/*z*): calcd for $C_{26}H_{35}O_4$ (M, H^+), 411.2535; found, 411.2539.

The enantiomeric ratio was determined by HPLC analysis (Chiralpak IC-3, hexane/isopropanol 98/02, flow rate= 0.5 mL/min, retention times: 45.0 min (minor) and 48.0 min (major)).

(*S*)-6-(5,5-Dibenzyl-1,3-dioxan-2-yl)-2-hydroxy-2,7-dimethyloctan-3-one (4Bc)

The title compound was obtained starting from isovaleraldehyde **1c** (43.1 mg, 0.5 mmol), α'-hydroxy enone **2B** (171.2 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 160 mg, 73%. $[\alpha]_D^{26} = -8.22°$ (*c*=1.27, 94:6 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.23 (m, 8H), 7.04 – 7.01 (m, 2H), 4.32 (d, *J*=4.4 Hz,

1H), 3.89 (s,1H), 3.78 – 3.73 (m, 2H), 3.53 – 3.47 (m, 2H), 3.08 – 3.00 (m, 2H), 2.90 – 2.72 (m, 2H), 2.45 (s, 2H), 1.96 – 1.72 (m, 3H), 1.47 – 1.42 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H),0.94 (d, *J*=7.0 Hz, 3H) ,0.90 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.9, 137.8, 136.3, 131.1, 130.4, 128.2, 128.1, 126.5, 126.4, 104.4, 76.1, 73.0, 72.8, 47.7, 39.6, 39.3, 36.9, 35.1, 28.1, 26.6, 26.5, 20.7, 19.9, 19.1. MS (ESI, *m*/*z*): calcd for $C_{28}H_{39}O_4$ (M, H^+), 439.2848; found, 439.2852.

The enantiomeric ratio was determined by HPLC analysis (Chiralpak AD-3, hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 14.6 min (major) and 16.4 min (minor)).

(*R*)-6-(5,5-Dibenzyl-1,3-dioxan-2-yl)-2-hydroxy-2-methyldecan-3-ona (4Bd)

The title compound was obtained starting from hexanal **1d** (50.1 mg, 0.5 mmol), α'-hydroxy enone **2B** (171.2 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 158 mg, 70%. $[\alpha]_D^{26}$ = −4.26° (*c*=1.14, 95:5 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.23 (m, 8H), 7.04 – 7.01 (m, 2H), 4.28 (d, *J*=3.2 Hz, 1H), 3.86 (s,1H), 3.76 (d, *J*=11.2 Hz, 2H), 3.51 (dd, *J*=11.2 Hz, *J*=7.6 Hz, 2H), 3.08 (*J*=13.4 Hz, 1H), 3.02 (*J*=13.4 Hz, 1H), 2.78 – 2.70 (m, 2H), 2.46 (s, 2H), 1.96 – 1.87 (m, 1H), 1.80 – 1.71 (m, 1H), 1.64 – 1.51 (m, 2H), 1.40 (s, 3H), 1.39 (s, 3H), 1.37 – 1.29 (m, 5H), 0.94 – 0.90 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.7, 137.9, 136.3, 131.1, 130.4, 128.2, 128.1, 126.5, 126.3, 104.3, 76.1, 72.8, 72.7, 41.9, 39.6, 39.3, 37.0, 33.8, 29.5, 29.3, 26.6, 23.2, 23.0, 14.1. MS (ESI, *m*/*z*): calcd for $C_{29}H_{41}O_4$ (M, H^+), 453.3005; found, 453.3010.

The enantiomeric purity was determined by HPLC analysis (Phenomenex Amylose-1, hexane/ethanol 95/05, 0°C, flow rate= 1 mL/min, retention times: 13.9 min (major) and 15.0 min (minor)).

(*R*)-6-(5,5-Dibenzyl-1,3-dioxan-2-yl)-7-cyclohexyl-2-hydroxy-2-methylheptan-3-one (4Be)

The title compound was obtained starting from 3-cyclohexylpropanal **1e** (70.1 mg, 0.5 mmol), α'-hydroxy enone **2B** (171.2 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 200 mg, 81%. $[\alpha]_D^{27}$ = −1.74° (*c*=1.20, 95:5 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.23 (m, 8H), 7.04 – 70.02 (m, 2H), 4.27 (d, *J*=2.8 Hz, 1H), 3.86 (s,1H), 3.77 – 3.74 (m, 2H), 3.53 – 3.48 (m, 2H), 3.08 (d, *J*=13.4 Hz, 1H), 3.01 (d, *J*=13.4 Hz, 1H), 2.74 – 2.71 (m, 2H), 2.46 (s, 2H), 1.96 – 1.88 (m, 1H), 1.78 – 1.55 (m, 7H), 1.51 – 1.10 (m, 6H), 1.40 (s, 3H), 1.39 (s, 3H), 0.98 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.7, 137.9, 136.3, 131.1, 130.4, 128.2, 128.1, 126.5, 126.3, 104.5, 76.1, 72.9, 72.7, 39.6, 39.3, 38.7, 37.5, 37.0, 35.0, 33.9, 33.7, 33.4, 26.7, 26.6, 26.4, 26.3, 23.5. MS (ESI, *m*/*z*): calcd for $C_{32}H_{45}O_4$ (M, H^+), 493.3318; found, 493.3317.

The enantiomeric ratio was determined by HPLC analysis (Chiralpak AD-3, hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 10.2 min (major) and 11.6 min (minor)).

(*S*)-6-(5,5-Dibenzyl-1,3-dioxan-2-yl)-2-hydroxy-2-methylnon-8-en-3-one (4Bf)

The title compound was obtained starting from 4-hexenal **1f** (49.1 mg, 0.5 mmol), α'-hydroxy enone **2B** (171.2 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 164 mg, 75%. $[\alpha]_D^{20}$ = −4.20° (*c*=1.56, 95:5 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.22 (m, 8H), 7.04 – 7.02 (m, 2H), 5.88 – 5.77 (m, 1H), 5.10 – 5.03 (m, 2H), 4.30 (d, *J*=3.2 Hz, 1H), 3.82 (s,1H), 3.76 (d, *J*=11.4 Hz, 2H), 3.51 (dd, *J*=11.4 Hz, *J*=4.8 Hz, 2H), 3.07 (d, *J*=13.2 Hz, 1H), 3.02 (d, *J*=13.2 Hz, 1H), 2.77 – 2.70 (m, 2H), 2.46 (s, 2H), 2.41 – 2.34 (m, 1H), 2.19 – 2.11 (m, 1H), 1.94 – 1.85 (m, 1H), 1.80 – 1.71 (m, 2H), 1.39 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.5, 137.8, 136.9, 136.3, 131.1, 130.4, 128.2, 128.1, 126.5, 126.3, 116.4, 103.7, 76.1, 72.8, 72.7, 41.6, 39.5, 39.3, 37.0, 34.0, 33.6, 26.6, 22.9. MS (ESI, *m*/*z*): calcd for $C_{28}H_{37}O_4$ (M, H^+), 437.2692; found, 437.2697.

The enantiomeric ratio was determined by HPLC analysis (Chiralpak AD-3, hexane/isopropanol 95/05, flow rate= 1 mL/min, retention times: 13.4 min (major) and 14.7 min (minor)).

(*S*)-8-(Benzyloxy)-6-(1,3-dioxolan-2-yl)-2-hydroxy-2-methyloctan-3-one (3Bg)

The title compound was obtained starting from 4-benzyloxybutanal **1g** (89.1 mg, 0.5 mmol), α'-hydroxy enone **2B** (171.2 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 126 mg, 75%. $[\alpha]_D^{21}$ = −0.5° (*c*=0.39, 94:6 *er*, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.27 (m, 5H), 4.79 (d, *J*=3.6 Hz, 1H), 4.53 (d, *J*=12.0 Hz, 1H), 4.50 (d, *J*=12.0 Hz, 1H), 4.00 – 3.91 (m, 2H), 3.87 – 3.81 (m, 3H), 3.62 – 3.54 (m, 2H), 2.68 (t, *J*=7.4 Hz, 2H), 1.91 – 1.78 (m, 3H), 1.74 – 1.56 (m, 2H), 1.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.6, 138.5, 128.4, 127.7, 127.6, 106.6, 76.1, 72.9, 68.4, 64.9, 64.8, 38.1, 33.3, 29.5, 26.5, 23.3. MS (ESI, *m*/*z*): calcd for $C_{19}H_{29}O_5$ (M, H^+), 337.2015; found, 337.2011.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, hexane/isopropanol 95/05, flow rate=0.5 mL/min, retention times: 29.5 min (minor) and 34.2 min (major)).

(*S*)-6-(5,5-dibenzyl-1,3-dioxan-2-yl)-2-hydroxy-2-methylnon-8-yn-3-one (4Bh)

The title compound was obtained starting from pent-4-ynal **1h** (41.0 mg, 0.5 mmol), α'-hydroxy enone **2B** (171.2 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 169 mg, 78%. $[\alpha]_D^{27}$ = −4.16° (*c*=1.7, 96:4 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.23 (m, 8H), 7.04 – 7.01 (m, 2H), 4.37 (d, *J*=3.6 Hz, 1H), 3.79 (s,1H), 3.75 (d, *J*=11.4 Hz, 2H), 3.52 (d, *J*=11.4 Hz, 2H), 3.02 (s, 2H), 2.84 – 2.69 (m, 2H), 2.49 (ddd, *J*=17.2 Hz, *J*=5.6 Hz, *J*=2.8 Hz, 1H), 2.46 (s, 2H), 2.36 (ddd, *J*=17.2 Hz, *J*=7.2 Hz, *J*=2.8 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.97 (t, *J*=2.8 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.40 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.2, 137.7, 136.2, 131.1, 130.4, 128.2, 128.1, 126.5, 126.4, 102.8, 82.6, 76.1, 72.8, 72.7, 69.6, 41.2, 39.5, 39.3, 37.0, 33.5, 26.6, 26.5, 23.1, 18.7. MS (ESI, *m*/*z*): calcd for $C_{28}H_{35}O_4$ (M, H^+), 435.2535; found, 435.2531.

The enantiomeric ratio was determined by HPLC analysis (Chiralpak AD-3, hexane/isopropanol 95/05, flow rate= 0.5 mL/min, retention times: 43.4 min (major) and 48.1 min (minor)).

(*S*)-6-(5,5-dibenzyl-1,3-dioxan-2-yl)-9-bromo-2-hydroxy-2-methylnonan-3-one (4Bi)

The title compound was obtained starting from 5-bromopentanal **1i** (82.5 mg, 0.5 mmol), α'-hydroxy enone **2B** (171.2 mg, 1.5 mmol) and the catalyst **C1** (32.5 mg, 0.1 mmol) as a colorless oil. Yield: 212 mg, 82%. $[\alpha]_D^{25}$ = −4.08° (*c*=0.92, 93:7 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.23 (m, 8H), 7.03 – 7.01 (m, 2H), 4.27 (d, *J*=3.2 Hz, 1H), 3.79 (s,1H), 3.75 (d, *J*=11.2 Hz, 2H), 3.50 (dd, *J*=11.2 Hz, *J*=4.4 Hz, 2H), 3.43 (t, *J*=6.8 Hz, 2H), 3.06 (d, *J*=13.4 Hz, 1H), 3.02 (d, *J*=13.4 Hz, 1H), 2.81 – 2.65 (m, 2H), 2.46 (s, 2H), 2.00 – 1.86 (m, 3H), 1.78 – 1.61 (m, 3H), 1.55 - 1.45(m, 1H), 1.40 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 214.5, 137.8, 136.2, 131.1, 130.4, 128.2, 128.1, 126.5, 126.4, 104.0, 76.2, 72.8, 72.7, 41.2, 39.7, 39.3, 36.9, 34.1, 33.5, 30.5, 28.1, 26.6, 23.2. MS (ESI, *m*/*z*): calcd for $C_{28}H_{38}BrO_4$ (M, H^+), 517.1953; found, 517.1958.

The enantiomeric ratio was determined by HPLC analysis (Chiralpak AY-3, hexane/isopropanol 95/05, flow rate= 0.5 mL/min, retention times: 14.4 min (minor) and 17.5 min (major)).

(*S*)-Methyl 4-(1,3-dioxolan-2-yl)-5-phenylpentanoate (6)

A suspension of sodium periodate $NaIO_4$ (321 mg, 1.5 mmol) in water (0.75 mL) was added to a solution of α-hydroxy ketone **3Ba** (87.7 mg, 0.3 mmol) in methanol (1.5 mL). The mixture was stirred at room temperature until the reaction was complete (monitored by TLC). Then the solvent was removed under reduced pressure. Water (4.5 ml) was added to the crude product and the resulting mixture was extracted with Et_2O (3 x 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated to afford the corresponding carboxylic acid. Then (trimethylsilyl)diazomethane (2M in hexane, 0.3 mL, 0.6 mmol) was added dropwise to a solution of carboxylic acid in a mixture of benzene (5 mL) and MeOH (0.5 mL) and the resulting solution was stirred 0.5 h at room temperature. The solvent was evaporated under reduced pressure to give the corresponding methyl ester which was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 10/1).

The title compound was obtained as a colorless oil. Yield: 63.4 mg, 80%. $[\alpha]_D^{21} = -4.41°$ (*c*=0.94, 97:3 *er*, $CHCl_3$). Lit[12e] for enantiomer $[\alpha]_D^{21} = +4.66°$ (*c*=0.87, 98:2 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 – 7.19 (m, 5H), 4.79 (d, *J*=3.6 Hz, 1H), 4.03 – 3.96 (m, 2H), 390 – 3.83 (m, 2H), 3.63 (s, 3H), 2.88 (dd, *J*=13.8 Hz, *J*=6.0 Hz, 1H), 2.58 (dd, *J*=13.8 Hz, *J*=8.4 Hz, 1H), 2.46 – 2.31 (m, 2H), 2.08 – 2.00 (m, 1H), 1.87 – 1.79 (m, 1H), 1.73 – 1.64 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.1, 140.1, 129.2, 128.3, 126.0, 105.6, 65.1, 64.9, 51.4, 42.7, 35.7, 32.1, 23.8. MS (ESI, *m/z*): calcd for $C_{15}H_{21}O_4$ (M, H^+), 265.1440; found, 265.1432.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, hexane/isopropanol 85/15, flow rate=0.5 mL/min, retention times: 19.6 min (major) and 30.3 min (minor)).

Elaboration of adduct (3Ba) into ketones (7) and (8). General procedure

MeLi (1.5 mmol) or nBuLi (1.5 mmol) was added to a solution of α'-hydroxy ketone **3Ba** (87.7 mg, 0.3 mmol) in dry THF (1.5 mL) at 0 °C and the resulting solution was stirred at room temperature until the reaction was complete (monitored by TLC). Then NH_4Cl (saturated solution, 3 mL) was added at 0 °C and the resulting mixture was extracted with CH_2Cl_2 (3 x 5 mL). The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with $NaIO_4$, under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 10/1).

(*S*)-5-(1,3-Dioxolan-2-yl)-6-phenylhexan-2-one (7)

Prepared according to the general procedure using MeLi (1.6 M in Et_2O, 0.94 mL, 1.5 mmol). The title compound was isolated as a colorless oil. Yield: 63.3 mg, 85%. $[\alpha]_D^{20} = -11.5°$ (*c*=0.7, 97:3 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.19 (m, 5H), 4.77 (d, *J*=3.6 Hz, 1H), 4.02 – 3.96 (m,2H), 3.92 – 3.84 (m,2H), 2.89 (dd, *J*=13.8 Hz, *J*=5.8 Hz, 1H), 2.06 – 1.98 (m, 1H), 2.58 – 2.39 (m, 3H), 2.06 (s, 3H), 2.04 – 1.96 (m, 1H), 1.82 – 1.73 (m, 1H) 1.67 – 1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 208.9, 140.2, 129.2, 128.3, 126.0, 105.8, 65.0, 64.9, 42.7, 41.7, 35.8, 29.7, 22.7. MS (ESI, *m/z*): calcd for $C_{15}H_{21}O_3$ (M, H^+), 249.1491; found, 249.1488.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, hexane/isopropanol 94/06, flow rate=1 mL/min, retention times: 14.6 min (major) and 24.1 min (minor)).

(*S*)-2-(1,3-Dioxolan-2-yl)-1-phenylnonan-5-one (8)

Prepared according to the general procedure using nBuLi (2.5 M in hexanes, 0.6 mL, 1.5 mmol). The title compound was isolated as a colorless oil. Yield: 75.8 mg, 87%. $[\alpha]_D^{19} = -12.4°$ (*c*=0.6, 97:3 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.18 (m, 5H), 4.77 (d, *J*=3.6 Hz, 1H), 4.02 – 3.94 (m,2H), 3.91 – 3.82 (m,2H), 2.89 (dd, *J*=14.0 Hz, *J*=5.8 Hz, 1H), 2.55 (dd, *J*=14.0 Hz, *J*=8.8 Hz, 1H), 2.50 – 2.35 (m, 2H), 2.31 (t, *J*=7.3 Hz, 2H), 2.03 – 1.96 (m, 1H), 1.81 – 1.72 (m, 1H), 1.66 – 1.57 (m, 1H), 1.54 – 1.47 (m, 2H), 1.33 – 1.23 (m, 2H), 0.90 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.2, 140.3, 129.2, 128.3, 126.0, 105.8, 65.0, 64.9, 42.7, 42.4, 40.7, 35.8, 25.9, 22.7, 22.4, 13.9. MS (ESI, *m/z*): calcd for $C_{18}H_{27}O_3$ (M, H^+), 291.1960; found, 291.1963.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, hexane/isopropanol 85/15, flow rate=0.5 mL/min, retention times: 19.1 min (major) and 29.4 min (minor)).

Elaboration of adducts (3Ba) and (4Bd) into aldehydes (9) and (10) respectively. General procedure

BH_3·THF complex (1 M, 0.6 mL, 0.6 mmol) was added to a solution of α'-hydroxy ketone (0.3 mmol) in dry THF (0.9 mL) at 0 °C and the resulting solution was stirred at the same temperature for 2 h. Then MeOH (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue thus obtained was subjected to oxidative scission by treatment with $NaIO_4$, under the same conditions reported above. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 20/1) to give the aldehyde as a colorless oil.

(*S*)-4-(1,3-Dioxolan-2-yl)-5-phenylpentanal (9)

Prepared according to the general procedure starting from α'-hydroxy ketone **3Ba** (87.7 mg, 0.3 mmol). The title compound was isolated as a colorless oil. Yield: 56.9 mg, 81%. $[\alpha]_D^{20} = -11.6°$ (*c*=1.3, 97:3 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.68 (t, *J*=1.6 Hz, 1H), 7.32 – 7.20 (m, 5H), 4.78 (d, *J*=3.6 Hz, 1H), 4.03 – 3.92 (m,2H), 3.90 – 3.83 (m,2H), 2.91 (dd, *J*=13.6 Hz, *J*=5.8 Hz, 1H), 2.56 (dd, *J*=13.6 Hz, *J*=8.8 Hz, 1H), 2.56 – 2.40 (m, 2H), 2.08 – 2.00 (m, 1H), 1.87 – 1.77 (m, 1H), 1.72 – 1.63 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.6, 140.0, 129.2, 128.4, 126.2, 105.6, 65.1, 64.9, 42.7, 42.0, 35.9, 20.8. MS (ESI, *m/z*): calcd for $C_{14}H_{19}O_3$ (M, H^+), 235.1334; found, 235.1328.

(*R*)-4-(5,5-Dibenzyl-1,3-dioxan-2-yl)octanal (10)

Prepared according to the general procedure starting from α'-hydroxy ketone **4Bd** (135.8 mg, 0.3 mmol). The title compound was isolated as a colorless oil. Yield: 88.8 mg, 75%. $[\alpha]_D^{20} = -2.9°$ (*c*=1.8, 95:5 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.79 (t, *J*=1.8 Hz, 1H), 741 – 7.23 (m, 8H), 7.04 – 7.02 (m, 2H), 4.28 (d, *J*=3.6 Hz, 1H), 3.76 (d, *J*=11.4 Hz, 2H), 3.51 (dd, *J*=11.4 Hz, *J*=6.6 Hz, 2H), 3.08 (d, *J*=13.4 Hz, 1H), 3.03 (d, *J*=13.4 Hz, 1H), 2.58 – 2.54 (m, 2H), 2.47 (s, 2H), 1.99 – 1.90 (m, 1H), 1.81 – 1.73 (m, 1H), 1.67 – 1.53 (m, 2H) 1.33 – 1.31 (m, 5H), 0.94 – 0.91 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.0,

137.9, 136.3, 131.1, 130.5, 128.2, 126.5, 126.3, 103.8, 72.7, 72.6, 42.1, 41.9, 39.7, 39.3, 37.0, 29.5, 28.8, 23.1, 21.3, 14.1. MS (ESI, *m/z*): calcd for $C_{26}H_{35}O_3$ (M, H^+), 395.2586; found, 395.2590.

Reduction of aldehydes (9) and (10) to alcohols (9') and (10') respectively. General procedure

Sodium borohydride (113 mg, 3mmol) was added to a solution of corresponding aldehyde (0.3 mmol) in MeOH (3 mL) at 0 °C. After 0.5 h of vigorous stirring at room temperature, saturated aqueous NH_4Cl (5 mL) was added. The resulting mixture was extracted with ethyl acetate (3 x 5 mL), the organic phases dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 10/1) to give the corresponding alcohol as a colorless oil.

(*S*)-4-(1,3-Dioxolan-2-yl)-5-phenylpentan-1-ol (9')

Prepared according to the general procedure starting from aldehyde **9** (70.3 mg, 0.3 mmol). The title compound was isolated as a colorless oil. Yield: 67.3 mg, 95%. $[\alpha]_D^{26}$ = +2.3° (*c*=0.53, 97:3 *er*, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.18 (m, 5H), 4.82 (d, *J*=3.6 Hz, 1H), 4.02 – 3.96 (m,2H), 3.93 – 3.86 (m,2H), 3.58 (t_b, *J*=6.0 Hz, 2H), 2.89 (dd, *J*=13.6 Hz, *J*=6.0 Hz, 1H), 2.59 (dd, *J*=13.6 Hz, *J*=8.4 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.66 – 1.51 (m, 4H), 1.43 – 1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.5, 129.2, 128.3, 125.9, 105.8, 65.1, 65.0, 63.0, 43.0, 35.7, 30.4, 24.5. MS (ESI, *m/z*): calcd for $C_{14}H_{21}O_3$ (M, H^+), 237.1491; found, 237.1485.

The enantiomeric ratio was determined by HPLC analysis (Chiralcel OD-H, hexane/isopropanol 94/06, flow rate=1 mL/min, retention times: 22.9 min (major) and 32.7 min (minor)).

(*R*)-4-(5,5-Dibenzyl-1,3-dioxan-2-yl)octan-1-ol (10')

Prepared according to the general procedure starting from aldehyde **10** (118.4 mg, 0.3 mmol). The title compound was isolated as a colorless oil. Yield: 113 mg, 95%. $[\alpha]_D^{19}$ = +2.9° (*c*=2.1, 95:5 *er*, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.23 (m, 8H), 7.03 – 7.01 (m,2H), 4.30 (d, *J*=2.8 Hz, 1H), 3.76 (d, *J*=11.4 Hz, 2H), 3.66 (t, *J*=6.2 Hz, 2H), 3.52 (dd, *J*=11.4 Hz, *J*=6.0 Hz, 2H), 3.09 (d, *J*=13.4 Hz, 1H) 3.04 (d, *J*=13.4 Hz, 1H), 2.46 (s, 2H), 1.71 – 1.57 (m, 6H), 1.46 – 1.27 (m, 6H), 0.93 – 0.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.0, 136.4, 131.2, 130.5, 128.2, 126.5, 126.3, 104.0, 72.7, 72.6, 63.2, 42.2, 39.7, 39.3, 37.0, 30.7, 29.7, 29.1, 25.0, 23.1, 14.1. MS (ESI, *m/z*): calcd for $C_{26}H_{37}O_3$ (M, H^+), 397.2743; found, 397.2749.

The enantiomeric ratio was determined by HPLC analysis (Phenomenex Cellulose-1, hexane/isopropanol 95/05, flow rate=1 mL/min, retention times: 23.6 min (minor) and 26.3 min (major)).

Author Contributions

C.P. and J.M.G. conceptualized the work. J.M.O., J.R. and B.L. performed all the experiments, M.O and A.M. helped with data interpretation and preparation of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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