ORIGINAL PAPER



# Highly stereoselective metal-mediated domino aldol reactions of propiophenone enolates with heteroaromatic, aliphatic, and unsaturated aldehydes

M. Emin Cinar<sup>1</sup> · Michael Schmittel<sup>1</sup>

Received: 5 July 2016/Accepted: 30 August 2016 © Springer-Verlag Wien 2016

**Abstract** The one-pot reaction of propiophenone with heteroaromatic, aliphatic, and unsaturated aldehydes in the presence of metal halides furnishes racemic tetrahydro-2*H*-pyran-2,4-diols in a highly diastereo-selective manner. The mechanism for the stereoselective product formation as well as the surprising formation of a side product was explained on the basis of DFT computations. *Graphical abstract* 

<sup>n</sup> Ph Me <u>1) LDA, 40 °C, 1 h</u> <u>2) MCIn, 40 °C, 30 min</u> Ph Me <u>RCHO</u> <u>40 °C, 2h</u> [THF] <u>Ph Me</u> Ph Me Ph Me Ph Me Ph Me Ph Me Ph Me

**Keywords** Tetrahydropyran · Enolates · Diastereo-selective reaction · Aldol reactions · Natural products · Density functional theory

### Introduction

The aldol reaction has extensively been used in the synthesis of natural products [1-3], in a multitude of stereoselective synthetic strategies [4-6], and in tandem protocols [7-11] due to its high synthetic utility for the carbon–carbon bond formation [12-15]. While standard

M. Emin Cinar emin.cinar@uni-siegen.de

Michael Schmittel schmittel@chemie.uni-siegen.de procedures generally only encompass one aldol step, tandem reactions with two consecutive aldol steps often end up with the trimerization of enolates [16, 17].

Metal (Ti, Zr, Si, and Sn) and boron enolates have achieved a considerable impact, because of their proven ability to control the stereochemical outcome of the C–C bond formation [18]. In contrast, other group 13 metal enolates have widely been neglected over the years [19–22]. Using a wide selection of metal centers, we have reported a domino aldol–aldol–hemiacetal process (Scheme 1) that furnishes racemic tetrahydro-2*H*-pyran-2,4-diols in a highly stereoselective manner via metal oligoenolates (2, 3, or 4 enolate residues) [18, 23–29].

In this paper, we evaluate the potential of this domino aldol–aldol–hemiacetal scheme to tolerate a range of aldehydes (heteroaromatic, aliphatic, and unsaturated aldehydes) while varying the metal centers (Al, In, Zr, and Sn). In addition, the process is assessed computationally.

### **Results and discussion**

#### Heteroaromatic aldehydes

To probe aldehydes with additional donor sites, a small series of heteroaromatic aldehydes (3b-3f) were investigated (Scheme 2; Table 1).

Despite several attempts with 2-pyridinaldehyde (3d), no domino-aldol product was afforded as the reaction stopped at the mono aldolate. Pleasingly, with 3- and 4-pyridinecarboxaldehydes (3e and 3f), the domino products 5e and 5f were obtained smoothly as single diastereomers with the same relative configuration as in 5a, respectively. In contrast, the reaction with 2- and 3-furfural (3b and 3c) led to the formation of the diastereomerically

<sup>&</sup>lt;sup>1</sup> Department Chemie-Biologie, Universität Siegen, Adolf-Reichwein-Str. 2, 57068 Siegen, Germany



Table 1 Reactions of various heteroaromatic aldehydes 3a-3f with propiophenone (1) enolate

			Yield /%					
Prod.	RCHO	AlCl <sub>3</sub>	InCl <sub>3</sub>	SnCl <sub>4</sub>	ZrCl <sub>4</sub>			
5a	⟨⊃→ ( 3a	64 <sup>a</sup>	85 <sup>a</sup>	36 (+29) <sup>b,c</sup>	76 <sup>°</sup>			
5b	Contraction of the second seco	40 (+10) <sup>b</sup>	51 (+25) <sup>b</sup>	27	53 (+25) <sup>b</sup>			
5c	S→→ 3c <sup>H</sup>	-	46 (+21) <sup>b</sup>	-	47 (+23) <sup>b</sup>			
5d	$\overset{N}{\underset{3d}{\overset{O}}}$	-	_d	-	_d			
5e	$\bigvee_{3e}^{N} \xrightarrow{O}_{H}$	-	52	-	45			
5f	NH	-	50	-	47			

<sup>a</sup> Ref. [25]

<sup>b</sup> rac-5a in the product

<sup>c</sup> Ref. [28]

<sup>d</sup> Only mono aldol product

pure products **5b** and **5c** as well as unexpectedly to the formation of **5a**. The ESI-MS spectrum showed signals at m/z = 397 and 387 Da that could be assigned to dominoaldol products **5a** and **5b** as (M + Na<sup>+</sup>), thus both associated with sodium cations.

A special situation emerged with 2-furfural (**3b**) as an electrophile as, in this case, a mixture of C3 epimers formed with the methyl group being in the equatorial (**5b**)

and axial position (**5b**') (Scheme 3). To understand the formation of diastereomer **5b**' more closely, the reaction of the aluminum tris(propiophenone enolate) with 2-furfural (**3b**) was investigated varying the conversion (Table 2) and the temperature (Table 3). In the time dependence study at room temperature (Table 2), the ratio of **5b**:**5b**' (4:1) remained constant. In contrast, in the temperature dependence study, the ratio **5b**:**5b**' increased from 2:1 at -20 °C to 5:1 at 50 °C (Scheme 4; Table 3).

The formation of **5b**' possessing a methyl group in the axial position may be attributed to the ability of the furan oxygen in **3b** to act as a donor in the aldol reactions. The results of DFT calculations at M06/6-31G(d)/-LANL2DZ// B3LYP/6-31G(d)/LANL2DZ level are shown in Scheme 5. Throughout the computations, hexa-coordination at the aluminum center was used, which required filling the remaining coordination sites with THF molecules.

According to the computations, the 2-furfural (3b) first coordinates to the aluminum trisenolate E in an endergonic step affording complex C. One enolate subunit in C reacts with the aluminum-activated subunit 3b furnishing the anti-aldolate A1 in a downhill process liberating 82.0 kJ mol<sup>-1</sup>. The second aldol reaction affords u, l-A2 or *u*,*u*-A2, both having a chair conformation in processes that are downhill by 30 and 2.9 kJ mol<sup>-1</sup>. Finally, the thermodynamically less stable hemiacetals A3 and A3' are formed in a chair conformation, while the metalladioxane ring adopts a half-chair conformation. The DFT calculations indicate the absence of coordination between the ring oxygen of furfural (3b) and Al throughout all the steps. The computational results suggest that the metal-bound hemiacetals A3 and A3' are not direct precursors to the dominoaldol products 5b and 5b'. Because the second aldol

Highly stereoselective metal-mediated domino aldol reactions of propiophenone enolates with...



Table 2 Time dependence of the domino reaction with  $AlCl_3$  using benzaldehyde (3a) or furfural (3b) at room temperature

Time/ min	Yield/% with 2-furfural		Yield/% with benzaldehyde		
	5b	<b>5</b> b′ <sup>a</sup>	5a	6a	
10	21	5	34	14	
20	23	6	37	12	
40	27	7	40	10	
80	36	9	56	9	
120	40	10	65	8	

<sup>a</sup> **5b**' is a C3 epimer of the **5b** 

reaction in this cascade affords the, thermodynamically, most stable products, i.e., u,l-A2 and u,u-A2, we expect that their hydrolysis will provide the end products **5b** and **5b**'. This suggestion is equally in alignment with the increase of the products ratios from 2:1 to 4:1 at higher temperature.

### Aliphatic and unsaturated aldehydes

To further probe the synthetic versatility, aliphatic aldehydes 3 g-3 k were utilized (Scheme 2; Table 4). Despite the fact that these enolizable electrophiles are much more critical, tetrahydropyran-2,4-diols were furnished in yields up to 47 %. Again, in the all cases, the yields are higher with the larger indium than with aluminum. Notably, with aliphatic aldehydes, always two minor diastereomers were additionally observed beside the main product. For example, in the reaction with InCl<sub>3</sub> and isobutyraldehyde (3 h), the main product 5 h was afforded in 33 % yield accompanied by two diastereomers (11 and 3 % yields) (Table 4).

In the reactions of aldehydes with  $\alpha$ -hydrogens, such as butyraldehyde (**3** g) and (-)-myrtenal (**3** k), the standard product **5a** is also formed additionally, sometimes even exclusively. A plausible explanation for this transformation invokes an intramolecular hydrogen shift, analogous to the

Table 3 Temperature dependence of the reaction with  $AlCl_3$  using 2-furfural (3b) (time = 2 h)

Temperature/°C	5b	<b>5</b> b <sup>′a</sup>	6b <sup>b</sup>	6bc <sup>c</sup>
-40	3	_	66	_
-20	11	6	44	-
0	29	13	33	_
25	40	10	30	_
40	23	6	11	11
50	22	4	12	19

<sup>a</sup> **5b**' is a C3 epimer of **5b** 

<sup>b</sup> Ref. [30]

<sup>c</sup> Ref. [31]

Meerwein–Ponndorf–Verley (MPV) [32] reaction, whose transition state (**TS**) has a relative energy of 130 kJ mol<sup>-1</sup> with respect to **Me-Aldol** in the reaction of propiophenone enolate and butyraldehyde (for the calculation, acetaldehyde was considered). The newly generated aldolate **Ph-Aldol**, more stable than **Me-Aldol** by 4.64 kJ mol<sup>-1</sup>, is considered to undergo a retro-Aldol process giving rise to the benzaldehyde coordinated **PhCHO Complex** (Scheme 6).

### Conclusion

The present results demonstrate a domino-aldol reaction of heteroaromatic, aliphatic, and unsaturated aldehydes with several metals that is far superior to the method with TiCp<sub>2</sub> [17]. While the reaction with 2-furfural (**3b**) results not only in the anticipated product **5b**, but also in its C3-epimer **5b**', aldehydes with  $\alpha$ -hydrogen provide a mixture of three diastereomers along with the standard benzaldehyde product *rac*-**5a**. The phenomena observed with furfural and butyraldehyde were rationalized using DFT-level computations, which suggest a Meerwein–Ponndorf–Verley

Scheme 4 ОН |ОН Me  $\label{eq:Me} \int Me \quad \frac{1) \text{ LDA, THF, -40 °C, 1 h}}{2) \text{ AlCl}_3, \text{ THF, -40 °C, 30 min}}$ Мe 5b 5b' 3 Ph 0 OH Ph 3) **3**) **3**) **3**) **3**) **3**) **4** THF, 2 h, **3**) **3**) **3**) **3**) **3**) **4** HF, 2 h, **4** Variable Temp. Мe Мe 6b 6bc Scheme 5 Ph 3b H Complexation Me R<sub>N</sub>Me 1. aldol 0 - Al-Me addition THF 3 Ο Me Ph Enolate (E)+3THF Complex (C) + THF **A1** -82.0 0.00 -9.16 1 2. aldol addition 2. aldol addition Ph Ph Me Me P S S S Me Me Мe Ŵе u,/**-A2** u,u**-A2** -112 -84.9 hemiacetal formation hemiacetal formation Ph Me Мe Ме R R Chair Мe Chair Conformation Conformation A3' A3 -76.6 -64.4 hydrolysis hydrolysis

5b'

Table 4	Reactions	of	various	aliphatic	and	unsaturated	aldehydes
3 g–3 k	with propic	ophe	enone (1	) enolate			

		Yield /%				
Product	RCHO	AlCl <sub>3</sub>	InCl <sub>3</sub>	SnCl <sub>4</sub>	ZrCl <sub>4</sub>	
5g	с₃н <sub>7</sub> –⋞ 3g <sup>н</sup>	17 <sup>a,c</sup>	37 <sup>a</sup>	18	12	
5h	)⊣ <rb></rb>	21 <sup>a</sup>	47 <sup>a</sup>	33	-	
5i	3i H	-	21 <sup>b</sup>	-	15	
5j	⟨H 3j	4	11	31	-	
5k	Sk H	-	13 <sup>c</sup>	-	5	

<sup>a</sup> Three diastereomers

<sup>b</sup> 1:1.4 mixture of *rac*-5i and *rac*-5a

<sup>c</sup> 1:5 mixture of *rac*-5k and *rac*-5a

<sup>d</sup> (-)-Myrtenal

(MPV) analogous intramolecular hydride shift followed by a retro-aldol reaction. The variations in the metal fragment are promising with regard to the development of an enantioselective version of the above reaction and further variations in the substrates.

### Experimental

Starting materials were purchased from Acros Organics, Aldrich, Merck, or Lancaster, and used as received. Aldehydes were distilled if necessary. Standard inert

Scheme 6

atmosphere and Schlenk techniques were employed for all reactions. THF was distilled under nitrogen directly over potassium. <sup>1</sup>H NMR and <sup>13</sup>C NMR were measured on a Bruker AC 200 (200 MHz) or AC 400 (400 MHz). All the NMR measurements were carried out at room temperature in CDCl<sub>3</sub>; chemical shifts refer to tetramethylsilane. IR spectra were recorded on a Perkin-Elmer FT-IR 1605. Elemental analyses were performed on a Carlo Erba Elemental Analyzer 1106. Uncorrected melting points were determined by using a Mettler FP5.0. Purification of compounds was performed using HPLC quipped with RP-18 Lichrosorb column.

### Computation

DFT calculations were performed using the Gaussian 09 [33]. B3LYP [34–36] was employed with Pople's splitvalence 6-31G(d) basis set on C, H, and O atoms and double- $\zeta$  quality basis set (LANL2DZ) [37–39] containing Hay and Wadt's effective core potential (ECP) on hexacoordinate aluminum (aluminum trichloride forms AlCl<sub>3</sub>. (THF)<sub>3</sub> complex in THF [40]). The remaining coordination sites of metals were occupied by THF molecules. The minima of the calculated structures were verified by analyzing the harmonic vibrational frequencies using the analytical second derivatives, which have NImag = 0. Single-point calculations with M06 functional [41] were performed using the same basis sets.

### **General procedure**

Synthesis of racemic tetrahydro-2*H*-pyrans was realized according to a literature procedure given in Ref. [29]. To a solution of lithium diisopropylamide, which was prepared from 1.26 cm<sup>3</sup> diisopropylamine (9.00 mmol) in 30 cm<sup>3</sup> THF with 3.00 cm<sup>3</sup> of *n*-butyllithium (2.5 M in *n*-hexane, 7.50 mmol) at 0 °C, was added 1.01 cm<sup>3</sup> propiophenone (1, 7.50 mmol) at -40 °C and the mixture was stirred for 1 h at the same temperature. Then, 2.5 mmol of the metal halide were introduced and the resulting yellow reaction mixture was stirred for 30 min at -40 °C and for 1 h at



room temperature. After the treatment of the metal enolate with a solution of 250 mg benzaldehyde (**3a**, 2.50 mmol) in 30 cm<sup>3</sup> of THF, the mixture was stirred at the given reaction temperature for 2 h (see Tables in manuscript). It was quenched with 50 cm<sup>3</sup> saturated NH<sub>4</sub>Cl<sub>(aq)</sub> solution and the aqueous layer was extracted three times with 30 cm<sup>3</sup> diethyl ether. The combined organic phases were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>.

In the case of  $ZrCl_4$ : The aldehyde was added in neat. The overall amount of THF was 30 cm<sup>3</sup>. In the case of SnCl<sub>4</sub>: 5.00 mmol of lithium diisopropylamide were reacted with 660 mm<sup>3</sup> of propiophenone (5.00 mmol).

### (*l*,*l*,*l*,*u*)-6-(*Furan*-2-*yl*)-3,5-dimethyl-2,4-diphenyltetrahydro-2H-pyran-2,4-diol (**5b**) [26]

AlCl<sub>3</sub> (333 mg, 2.50 mmol), 555 mg InCl<sub>3</sub> (2.50 mmol) and 583 mg ZrCl<sub>4</sub> (2.50 mmol) were used as coordination metals in separate experiments in combination with a solution of 210 mm<sup>3</sup> furfural (**3b**, 2.50 mmol) in 30 cm<sup>3</sup> THF. The crude product was purified by HPLC methanol/ water (4:1) affording with AlCl<sub>3</sub> 364 mg (1.00 mmol, 40 %), with InCl<sub>3</sub> 465 mg (1.28 mmol, 51 %), and with ZrCl<sub>4</sub> 485 mg (1.33 mmol, 53 %) of **5b** as a colorless solid. M.p.: 160 °C. The results of the spectroscopic measurements are well in agreement with the reported ones.

### (u,u,l,u)-6-(Furan-2-yl)-3,5-dimethyl-2,4-diphenyltetrahydro-2H-pyran-2,4-diol (**5b**', C<sub>23</sub>H<sub>24</sub>O<sub>4</sub>) [26]

In a second fraction, we obtained for aluminum(III) chloride 91.0 mg (250 µmol, 10 %) and with indium(III)-chloride 228 mg (625 µmol, 25 %) and with zirconium(IV) chloride 228 mg (625 µmol, 25 %) of **5b**' as a colorless solid. M.p.: 185 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta = 0.44$  (d, J = 6.8 Hz, 3H), 0.59 (d, J = 7.0 Hz, 3H), 2.36 (m, 2H), 3.81 (d, J = 1.7 Hz, 1H), 3.91 (s, 1H), 5.05 (d, J = 10.8 Hz, 1H), 6.34 (d, J = 2.0 Hz, 1H), 7.18–7.40 (m, 7H), 7.49 (m, 2H), 7.70 (m, 3H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta = 9.4$ , 10.6, 43.6, 47.7, 68.7, 78.1, 101.7, 123.8, 126.0, 126.3, 126.6, 127.7, 128.0, 128.2, 128.3, 142.3, 143.0, 144.0, 153.4 ppm; and IR (KBr):  $\bar{v} = 3394$ , 3090, 3061, 3029, 29726, 2941, 1602, 1533, 1455, 1446, 1388, 1378, 1314, 1226, 1152, 1135, 1074, 1058, 1034, 1028, 1016, 1005, 997, 967, 699 cm<sup>-1</sup>.

# (*E*)-3-(*Furan*-2-*y*l)-2-*methyl*-1-*phenylprop*-2-*en*-1-*one* (**6bc**)

The results of the spectroscopic measurements are in agreement with the literature values [31].

# (l,l,l,u)-6-(Furan-3-yl)-3,5-dimethyl-2,4-diphenyltetrahydro-2H-pyran-2,4-diol (**5c**, C<sub>23</sub>H<sub>24</sub>O<sub>4</sub>)

InCl<sub>3</sub> (555 mg, 2.50 mmol) and 583 mg  $ZrCl_4$  (2.50 mmol) were added as coordination metals in separate experiments. A solution of 210 mm<sup>3</sup> 3-furanal (**3c**,

2.50 mmol) in 30 cm<sup>3</sup> THF was added. The crude product was purified by HPLC using methanol/water (4:1) as eluent providing with InCl<sub>3</sub> 419 mg (1.15 mmol, 46 %) and with  $ZrCl_4$  428 mg (1.18 mmol, 47 %) of **5c** as a colorless solid. M.p.: 164 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 0.49$  (d, J = 6.8 Hz, 3H), 0.56 (d, J = 7.1 Hz, 3H), 2.32 (qd, J = 7.1, 1.2 Hz, 1H), 2.70 (qd, J = 6.8, 10.8 Hz, 1H), 3.83 (s, 1H), 4.05 (d, J = 1.2 Hz, 1H), 5.14 (d, J = 10.8 Hz, 1H), 6.34 (dd, J = 3.3, 2.0 Hz, 1H), 6.38 (dd, J = 3.3, 0.8 Hz, 1H), 7.32–7.38 (m, 4H), 7.43 (dd, J = 2.0, 0.8 Hz, 1H), 7.49 (m, 2H), 7.61–7.65 (m, 2H), 7.70 (m, 2H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta = 9.5$ , 10.8, 46.6, 47.9, 75.6, 78.1, 101.8, 106.4, 111.2, 125.8, 126.4, 126.7, 127.7, 128.0, 128.2, 128.4, 143.3, 143.4, 145.2 ppm; and IR (KBr):  $\bar{v} = 3394$ , 3090, 3061, 3029, 2976, 2941, 1602, 1533, 1455, 1446, 1388, 1378, 1314, 1226, 1152, 1135, 1074, 1058, 1034, 1028, 1016, 1005, 997, 967, 699  $\text{cm}^{-1}$ .

### (l,l,l,u)-3,5-Dimethyl-2,4-diphenyl-6-(pyridin-3-yl)tetrahydro-2H-pyran-2,4-diol (**5e**, C<sub>24</sub>H<sub>25</sub>NO<sub>3</sub>)

As coordination metals 555 mg InCl<sub>3</sub> (2.50 mmol) and 583 mg ZrCl<sub>4</sub> (2.50 mmol) were used. 3-Pyridinecarboxaldehyde (3e, 236 mm<sup>3</sup>, 2.50 mmol) was added. The crude product was recrystallized from *n*-hexane furnishing 488 mg (1.30 mmol, 52 %) and 422 mg (1.13 mmol, 45 %) of **5e** as a colorless solid using InCl<sub>3</sub> and ZrCl<sub>4</sub>. respectively. M.p.: 174 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta = 0.41$  (d, J = 6.6 Hz, 3H), 0.59 (d, J = 6.9 Hz, 3H), 2.25-2.40 (m, 2H), 4.83 (s, 1H), 5.09 (d, J = 10.6 Hz, 1H),7.20–7.45 (m, 4H), 7.66 (d, J = 7.1 Hz, 2H), 7.66 (d, J = 7.1 Hz, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 4.7 Hz, 1H), 7.53–7.60 (m, 3H), 8.51 (s, 1H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta=9.5,\,10.6,\,46.5,\,47.9,\,74.4,\,77.9,\,101.6,\,122.9,\,123.6,\,$ 125.9, 126.6, 127.7, 128.0, 128.2, 128.3, 132.2, 143.3, 143.9, 149.1, 150.2 ppm; and IR (KBr):  $\bar{v} = 3376$ , 3025, 2978, 2931, 1602, 1585, 1446, 1229, 1160, 1054, 1021, 1001, 965, 814, 750, 701, 621  $\text{cm}^{-1}$ .

# (l,l,l,u)-3,5-Dimethyl-2,4-diphenyl-6-(pyridin-4-yl)tetrahydro-2H-pyran-2,4-diol (**5f**, C<sub>24</sub>H<sub>25</sub>NO<sub>3</sub>)

As coordination metals 555 mg InCl<sub>3</sub> (2.50 mmol) and 583 mg ZrCl<sub>4</sub> (2.50 mmol) were used. 4-Pyridinecarboxaldehyde (**3f**, 236 mm<sup>3</sup>, 2.50 mmol) was added. The crude product was purified by crystallization from *n*-hexane furnishing 469 mg (1.25 mmol, 50 %) of **5f** using InCl<sub>3</sub> and 443 mg (1.18 mmol, 47 %) of **5f** in the presence of ZrCl<sub>4</sub> as a colorless solid. M.p.: 204 °C (decomp.); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta = 0.43$  (d, J = 6.9 Hz, 3H), 0.58 (d, J = 7.1 Hz, 3H), 2.15–2.40 (m, 2H), 4.53 (s, 1H), 5.00 (d, J = 10.3 Hz, 1H), 7.15–7.46 (m, 10H), 7.63–7.78 (m, 4H), 8.38 (s, 1H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta = 9.6$ , 10.6, 46.3, 47.9, 73.1 (2C), 101.6, 123.6, 124.0, 126.0, 126.4, 127.9, 128.0, 135.6, 143.7, 144.3, 148.5, 148.7 ppm; and IR (KBr):  $\bar{\nu} = 3388$ , 3060, 3035, 2977, 2941, 1602, 1447, 1387, 1225, 1135, 1059, 1034, 1015, 999, 968, 820, 777, 701, 630, 552 cm<sup>-1</sup>.

### (*l*,*l*,*l*)-3,5-Dimethyl-2,4-diphenyl-6-propyltetrahydro-2Hpyran-2,4-diol (**5g**, C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>) [25]

The following amounts of metal chloride have been used: 333 mg AlCl<sub>3</sub> (2.50 mmol), 555 mg InCl<sub>3</sub> (2.50 mmol), 583 mg  $ZrCl_4$  (2.50 mmol), and 326 mg SnCl₄ (1.25 mmol). *n*-Butyraldehyde (**3g**, 136 mg, 2.50 mmol) was reacted. The crude product was recrystallized from ethanol providing with AlCl<sub>3</sub> 76.6 mg (225 µmol, 9 %), with  $InCl_3$  136 mg (400  $\mu$ mol, 16 %), with  $ZrCl_4$ (300  $\mu$ mol, 12 %), and with SnCl<sub>4</sub> 153 mg (450  $\mu$ mol, 18 %) of 5g as a colorless solid. M.p.: 161 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta = 0.52$  (d, J = 7.1 Hz, 3H), 0.64 (d, J = 6.7 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H), 1.45–1.77 (m, 4H), 2.10 (qd, J = 10.3, 6.7 Hz, 1H), 2.36 (dq, J = 7.1, 1.2 Hz, 1H), 3.68 (s, 1H), 3.72 (d, J = 1.2 Hz, 1H), 4.11 (ddd, J = 10.3, 7.1, 3.0 Hz, 1H), 7.11-7.17 (br m, 1H),7.21 (tt, J = 7.3, 1.2 Hz, 1H), 7.27–7.38 (m, 5H), 7.60– 7.62 (m, 2H), 7.64–7.68 (m, 1H) ppm; <sup>13</sup>C NMR (50 MHz,  $CDCl_3$ ):  $\delta = 9.6, 10.6, 14.3, 17.9, 35.1, 44.0, 47.8, 70.9,$ 78.3, 100.6, 123.8, 126.1, 126.3, 126.4, 127.8, 127.8, 128.2, 144.8 ppm; and IR (KBr):  $\bar{v} = 3439$ , 3405, 3090, 3058, 3031, 2983, 2953, 2929, 2907, 2865, 1496, 1458, 1446, 1392, 1377, 1229, 1143, 1114, 1074, 1050, 1034, 997, 965, 744, 699, 616 cm<sup>-1</sup>.

### (*l*,*l*,*l*)-6-Isopropyl-3,5-dimethyl-2,4-diphenyltetrahydro-2H-pyran-2,4-diol (**5h**) [25, 26]

The following amounts of metal chloride were used: 333 mg AlCl<sub>3</sub> (2.50 mmol), 555 mg InCl<sub>3</sub> (2.50 mmol), 583 mg ZrCl<sub>4</sub> (2.50 mmol), and 326 mg SnCl<sub>4</sub> (1.25 mmol). Isobutyraldehyde (**3h**, 136 mg, 2.50 mmol) was reacted. The crude product was purified by recrystallization from ethanol resulting in with AlCl<sub>3</sub> 93.6 mg (275  $\mu$ mol, 11 %), with InCl<sub>3</sub> 281 mg (825 mmol, 33 %), and with SnCl<sub>4</sub> 281 mg (825 mmol, 33 %) of **5h** as a colorless solid. M.p.: 56 °C. The spectroscopic measurements are well in agreement with the literature spectra.

### (l,l,l,l)-(E)-3,5-Dimethyl-2,4-diphenyl-6-(prop-1-enyl)tetrahydro-2H-pyran-2,4-diol (**5i**, C<sub>22</sub>H<sub>26</sub>O<sub>3</sub>)

As coordination metals 555 mg InCl<sub>3</sub> (2.50 mmol) and 583 mg ZrCl<sub>4</sub> (2.50 mmol) were chosen. Crotonic aldehyde (**3i**, 175 mg, 2.50 mmol) was reacted. The crude product was purified by crystallization from ethanol giving 178 mg (525 µmol, 21 %) and 127 mg (375 µmol, 15 %) of **5i** using InCl<sub>3</sub> and using ZrCl<sub>4</sub>, respectively. M.p.: 140 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta = 0.51$  (d, J = 7.1 Hz, 3H), 0.61 (d, J = 6.6 Hz, 3H), 1.73 (dd, J = 6.2, 1.2 Hz, 3H), 2.00–2.26 (m, 2H), 3.77 (s, 1H), 3.99 (s, 1H), 4.47 (dd, J = 10.3, 7.6 Hz, 1H), 5.60 (dd, J = 15.3, 7.6 Hz, 1H), 5.82 (dd, J = 15.3, 6.4 Hz, 1H), 7.10–7.32 (m, 4H), 7.46-7.54 (m, 2H), 7.57–7.71 (m, 4H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta = 9.5$ , 10.7, 23.8, 44.9, 47.6, 75.6, 78.1, 101.0, 123.7, 125.0, 126.4, 127.7, 128.0, 128.3, 129.8, 130.4, 140.7, 144.2 ppm; and IR (KBr):  $\bar{v} = 3396$ , 3058, 3032, 2977, 2941, 1677, 1600, 1497, 1447, 1387, 1313, 1229, 1156, 1135, 1075, 1030, 965, 921, 768, 746, 699, 614 cm<sup>-1</sup>.

### (*l*,*l*,*l*)-(*E*)-3,5-Dimethyl-2,4-diphenyl-6-styryltetrahydro-2H-pyran-2,4-diol (**5**j) [26]

AlCl<sub>3</sub> (333 mg, 2.50 mmol), 555 mg InCl<sub>3</sub> (2.50 mmol), and 652 mg SnCl<sub>4</sub> (2.50 mmol) were added as coordination metals. A solution of 310 mm<sup>3</sup> cinnamaldehyde (**3j**, 2.50 mmol) in 30 cm<sup>3</sup> THF was introduced. The crude product was purified by crystallization from ethanol furnishing with AlCl<sub>3</sub> 40.1 mg (100 µmol, 4 %), with InCl<sub>3</sub> 110 mg (280 µmol, 11 %), and with SnCl<sub>4</sub> 311 mg (776 µmol, 31 %) of **5j** as a colorless solid. M.p.: 163 °C. The spectra are matching well with the literature ones.

### (l,l,l,l)-6-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-3-yl)-3,5dimethyl-2,4-diphenyltetrahydro-2H-pyran-2,4-diol (**5k**, C<sub>28</sub>H<sub>34</sub>O<sub>3</sub>)

As coordination metals 555 mg InCl<sub>3</sub> (2.50 mmol) and 583 mg ZrCl<sub>4</sub> (2.50 mmol) were added. (-)-Myrtenal (3 k, 376 mg, 2.50 mmol) was added. The crude product was purified by recrystallization from ethanol providing 136 mg (325  $\mu$ mol, 13 %) using InCl<sub>3</sub> and 52 mg (125 µmol, 5 %) in the presence of ZrCl<sub>4</sub>. M.p.: 167 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta = 0.52$  (d, J = 7.1 Hz, 3H), 0.60 (d, J = 6.9 Hz, 3H), 0.85 (s, 3H), 1.35 (s, 3H), 2.02–2.18 (m, 2H), 2.31 (d, J = 1.5 Hz, 2H), 2.42–2.62 (m, 2H), 3.74 (d, J = 1.2 Hz, 1H), 3.98 (s, 1H), 4.45 (d, J = 10.6 Hz, 1H), 5.59 (s, 1H), 7.10–7.42 (m, 7H), 7.51– 7.60 (m, 2H), 7.65–7.75 (m, 3H) ppm; <sup>13</sup>C NMR (50 MHz,  $CDCl_3$ ):  $\delta = 9.5, 10.7, 23.8, 26.5, 31.3, 32.0, 37.7, 40.4,$ 41.9, 42.6, 47.5, 75.6, 78.0, 100.9, 121.2, 123.7, 125.9, 126.3, 126.5, 127.7, 127.8, 128.1, 143.8, 144.7 ppm; and IR (KBr):  $\bar{v} = 3406, 3060, 2985, 2937, 1719, 1493, 1449,$ 1384, 1255, 1033, 997, 968, 770, 750, 701 cm<sup>-1</sup>.

Acknowledgments Financial support from the DFG (Graduiertenkolleg, SFB) and the Fonds der Chemischen Industrie is gratefully acknowledged. We are grateful to Dr. Thomas Koy and Wolfgang Henn for their valuable preparative work and helpful discussions in the early stage of this manuscript. We are indebted to the High-Performance-Computing (HPC) Linux Cluster HorUS of the University of Siegen for computational support.

### References

- 1. Kalesse M, Cordes M, Symkenberg G, Lu HH (2014) Nat Prod Rep 31:563
- 2. Shiina I (2014) Chem Rec 14:144

- 3. Raju KB, Kumar BN, Kumar BS, Nagaiah K (2015) Helv Chim Acta 98:386
- Braun M (1996) Simple diastereoselection and transition state models. In: Helmchen G, Hoffmann R, Mulzer J, Schaumann E (eds.), Houben-Weyl, E.21, Stereoselective Synthesis, Methods of organic chemistry, vol 3. Thieme Verlag, Stuttgart, p 1603
- 5. Ghorai MK, Halder S, Das S (2015) J Org Chem 80:9700
- 6. Ramesh P, Raju A, Fadnavis NW (2016) Helv Chim Acta 99:70
- 7. Wang X, Meng Q, Nation AJ, Leighton JL (2002) J Am Chem Soc 124:10672
- 8. Zhao BL, Liu L, Du DM (2014) Eur J Org Chem 2014:7850
- 9. Suman K, Thennarasu S (2015) RSC Adv 5:23291
- Han B, Huang W, Ren W, He G, Wang J, Peng C (2015) Adv Synth Catal 357:561
- 11. Okuma K, Itoyama R, Sou A, Nagahora N, Shioj K (2012) Chem Commun 48:11145
- 12. Nielsen AT, Houlihan WJ (1968) Organic Reactions, vol 16. Wiley, New York, p 1
- Mekelburger HB, Wilcox CS (1991) Formation of Enolates. In: Trost BM, Fleming I (eds) Comprehensive organic synthesis, vol 2. Pergamon Press, Oxford, p 99
- 14. Heathcock CH (1992) Modern enolate chemistry: regio- and stereoselective formation of enolates and the consequence of enolate configuration on subsequent reactions. In: Scheffold R (ed) Modern synthetic methods, vol 6. Verlag Helvetica Chimica Acta, Basel, p 1
- Mahrwald R (2009) Modern aldol reactions. Springer Science + Business Media BV, Heidelberg
- 16. Yun SS, Suh IH, Choi SS, Lee S (1998) Chem Lett 10:985
- 17. Pascal RA Jr, Mathai MS, Shen X, Ho DM (2001) Angew Chem Int Ed 40:4746
- Cinar ME, Schmittel M (2015) J Org Chem 80:8175 (And references therein)
- 19. Dénès F, Pérez-Luna A, Chemla F (2010) Chem Rev 110:2366
- 20. Bleschke C, Tissot M, Müller D, Alexakis A (2013) Org Lett 15:2152
- 21. Amemiya R, Yamaguchi M (2005) Eur J Org Chem 2005:5145
- 22. Thirupathaiah B, Seo SY (2015) Chem Commun 51:4216
- Schmittel M, Burghart A, Malisch W, Reising J, Söllner R (1998) J Org Chem 63:396
- Schmittel M, Burghart A, Werner H, Laubender M, Söllner R (1999) J Org Chem 64:3077

- Schmittel M, Ghorai MK, Haeuseler A, Henn W, Koy T, Söllner R (1999) Eur J Org Chem 1999:2007
- 26. Schmittel M, Ghorai MK (2001) Synlett 12:1992
- 27. Schmittel M, Haeuseler A, Nilges T, Pfitzner A (2003) Chem Commun 34
- 28. Haeuseler A, Henn W, Schmittel M (2003) Synthesis 16:2576
- 29. Cinar ME, Engelen B, Panthöfer M, Deiseroth HJ, Schlirf J, Schmittel M (2016) Beilstein J Org Chem 12:813
- Bartoszewicz A, Livendahl M, Martín-Matute B (2008) Chem Eur J 14:10547
- Žvak V, Kováč J, Dandárová M, Gracza T, Kríž M (1984) Collect Czech Chem Commun 49:1764
- Woodward RB, Wendlearn NL, Brutschy FJ (1945) J Am Chem Soc 67:1425
- 33. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery JA Jr, Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam JM, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas Ö, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ (2010) Gaussian 09. Gaussian Inc, Wallingford CT
- 34. Becke AD (1993) J Chem Phys 98:1372
- 35. Becke AD (1993) J Chem Phys 98:5648
- Lee C, Yang W, Parr RG (1988) Phys Rev B Condens Matter Mater Phys 37:785
- 37. Hay PJ, Wadt WR (1985) J Chem Phys 82:270
- 38. Wadt WR, Hay PJ (1985) J Chem Phys 82:284
- 39. Hay PJ, Wadt WR (1985) J Chem Phys 82:299
- Alves CC, Campos TBC, Alves WA (2012) Spectrochim Acta A Mol Biomol Spectrosc 97:1085
- 41. Zhao Y, Truhlar DG (2008) Theor Chem Acc 120:215