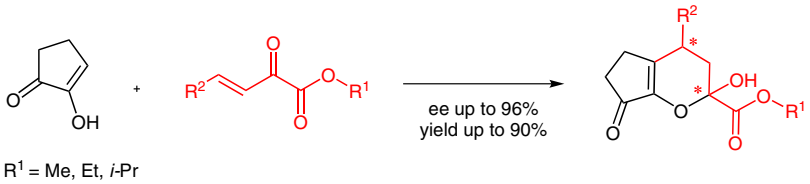
Synthesis G. Preegel et al. Paper

Enantioselective Organocatalytic Michael Addition–Cyclization Cascade of Cyclopentane-1,2-dione with Substituted (*E*)-2-oxobut-3-enoates

Gert Preegel[a]
Kaja Ilmarinen[a]
Ivar Järving[a]
Tõnis Kanger[a]
Tõnis Pehk[b]
Margus Lopp*[a]

[a] Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia
[b] National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia
margus.lopp@ttu.ee



R^1 = Me, Et, *i*-Pr
R^2 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl, cyclohexyl

Received: 27.06.2015
Accepted after revision: 28.08.2015
Published online: 01.10.2015
DOI: 10.1055/s-0035-1560347; Art ID: ss-2015-z0404.op

Abstract An organocatalytic cascade Michael addition-cyclization reaction of cyclopentane-1,2-dione with substituted (*E*)-2-oxobut-3-enoates, creating two stereocenters and giving bicyclic hemiacetals **3** in excellent yield (up to 93%) and enantioselectivity (up to 96% ee) was developed. From 2-chlorophenyl-substituted (*E*)-2-oxobut-3-enoate, the adduct revealed pseudo-atropisomerism from the hindered rotation of the phenyl ring. The hemiacetal **3** was reduced with Et_3SiH and Lewis acid affording substituted 1,2-cyclopentanedione **8**, and disilylated with an excess of TMSOTf and Et_3N to the dienol disilyl ether **9**.

Key words organocatalysis, cascade reactions, atropisomerism, stereoselectivity

Asymmetric organocatalytic cascade reactions, because of their efficiency and experimental simplicity, have been the focus of researchers for many years. Different nucleophiles and eletrophiles have been used to build various reaction cascades. Among the structural fragments, the 1,3-dicarbonyl compounds have been found suitable for different cascade reactions and, therefore, have been investigated thoroughly.[1–6] Thus, different cyclic 1,3-dicarbonyl compounds have been successfully used as nucleophiles with unsaturated[1] and saturated aldehydes,[2] with acetates of nitroalkenes,[3] with α-hydroxymethyl nitroalkenes,[4] with β-formyl esters,[5] and with α,β-unsaturated N-acylated succinimides.[6]

In contrast, 1,2-dicarbonyl compounds have received little attention. There are only a few examples of the use of cyclohexane-1,2-dione: nucleophilic additions to aldehydes,[7] nitroalkenes,[8] and keto esters.[9] Similar 2-hydroxy-1,4-naphthoquinones have also been used as Michael donors with keto esters.[10] For cyclopentane-1,2-dione there is only one example of the reaction with nitrostyrenes.[11] Additionally, the reaction with α,β-unsaturated aldehydes with cyclopentane-1,2-dione dienolate was described by our group recently.[12]

Many research groups have reported the usefulness of 2-oxobut-3-enoates substituted 1,2-dicarbonyl compounds in various reactions.[13] These compounds when acting as Michael acceptors afford different cyclic structures of interest: 3-substituted indoles,[14] 4-hydroxycoumarins,[15] hemiacetal esters,[16] and amino acid derivatives from isocyanides.[17] In addition, these compounds undergo organocatalytic cascade aldol reaction with 1,3-dicarbonyl compounds giving a bicyclic pyran derivative,[18] a hetero-Diels–Alder reaction with aldehydes[19] and dihydropyrans.[20] Similar pyran substructural units have been previously synthesized via Nazarov cyclization[20] and by a tandem Nazarov cyclization–Michael addition sequence.[21] Substituted pyrans and similar structural units are present in several antiviral ingredients, being valuable intermediates in the synthesis of bioactive compounds.[22]

In this article, we present our results on a cascade reaction of cyclopentane-1,2-dione (**1**) with substituted α-keto esters **2** giving novel bicyclic pyran derivatives **3** in excellent yields and stereoselectivities.

In organocatalysis, hydrogen bonding catalysis has been widely studied in recent years,[23] because of its evident benefits: high catalytic output, stability in air and water, and reusability. Similar to aminocatalysts, the H-bonding catalysts activate carbonyl groups in chemical reactions. In our case, four carbonyl groups are present in the reaction of α,β-unsaturated keto esters with cyclopentane-1,2-dione in which two pairs of them are in vicinal position. Therefore, bifunctional hydrogen bonding catalysts, activating both electrophile and nucleophile, seemed a reasonable choice from the group of the organocatalysts.

The preliminary results of the cascade reaction with cyclopentane-1,2-dione (**1**) with phenyl-substituted keto ester **2a** by using Soos's type organocatalyst **4a** in toluene were promising, affording hemiacetal **3a** in 35% yield with excellent stereoselectivity (96% ee, Table 1, entry 1) in a very short reaction time (15 min). The formation of predominantly only one diastereomer was observed.

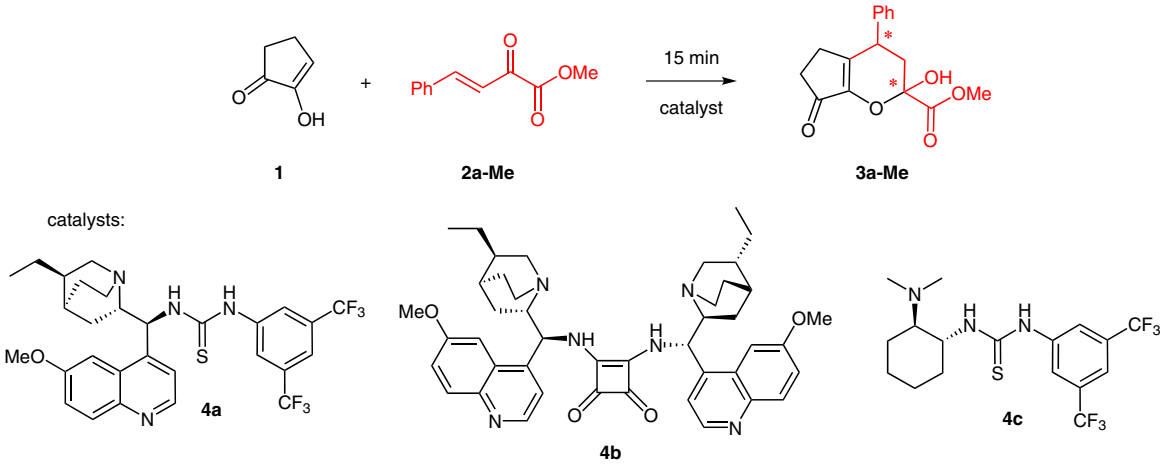
To find the optimal reaction conditions, a model reaction with cyclopentane-1,2-dione (**1**) and phenyl-substituted keto ester **2a-Me** was screened using different catalysts and solvents. The results are presented in Table 1.

We found that with catalyst **4a** the stereoselectivity of the reaction did not notabaly depend on the solvent; the stereoselectivity in toluene, dichloromethane, $CHCl_3$, and THF was almost equal. However, the best yields of product **3** were obtained in dichloromethane (Table 1, entries 1–4). Therefore, the screening of the catalysts was made using dichloromethane as the solvent. All of the used H-bonding catalysts resulted in very high stereoselectivity in the reaction. The best yield of product **3a** (89%) was obtained with the Takemoto-type catalyst **4c** (loading of 5 mol%), also affording excellent stereoselectivity (96% ee) in a very short reaction time (15 min, entry 6).

We propose that the reaction proceeds according to a pathway presented in Scheme 1, where one of the 1,2-dicarbonyl compounds, 1,2-cyclopentanedione (**1**), acts as a nucleophile and the other, 2-oxobut-3-enoate **2a-Me**, as an electrophile, both activated by the catalyst.

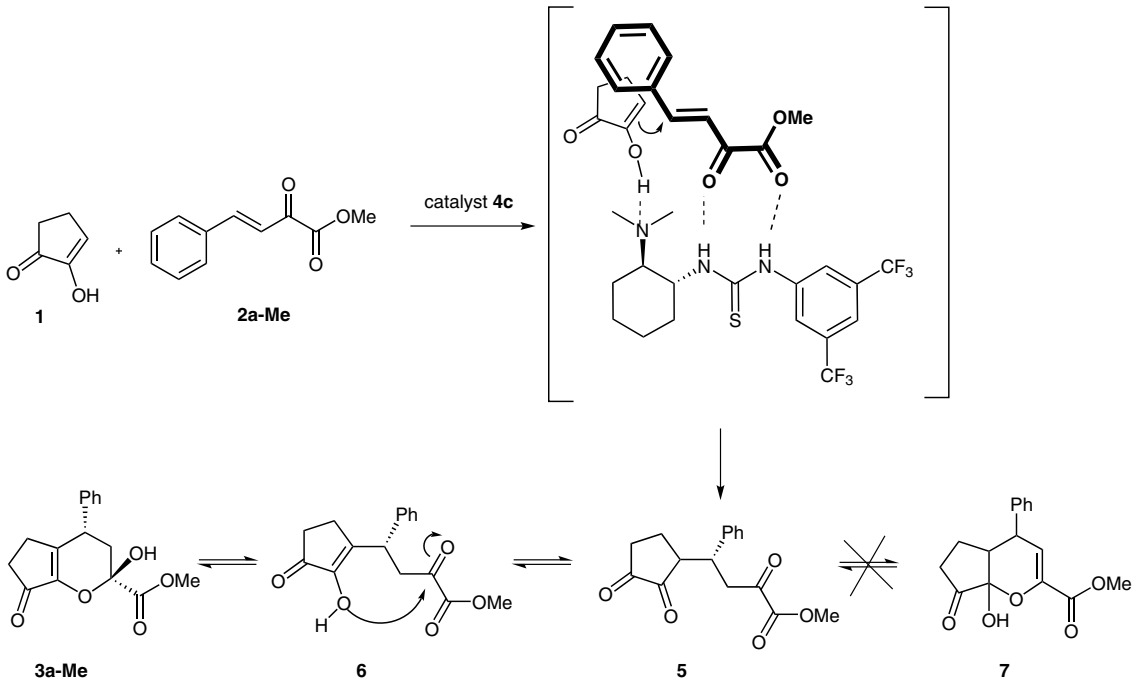
First, a Michael addition of the cyclopentane-1,2-dione (**1**) (in keto–enol form) to α,β-unsaturated keto ester **2a-Me** takes place, forming an adduct **5** (in equilibrium with its enol tautomer **6**). The Michael acceptor is activated via hydrogen bonds of the thiourea catalyst. At the same time, the tertiary amino group of the bifunctional catalyst **4c** acts as a hydrogen bond, acceptor shifting the equilibrium of cyclic diketone **1** towards the nucleophilic enol form. Because of keto–enol tautomerism, only one stereogenic center is formed in the first step of the cascade. In the preferred transition state, the *si*-face of the acceptor is favored, affording product in *R*-configuration. The following stereoselective cyclization of **5** (*R*-configuration) via hemiacetalization of enol **6** (*S*-configuration) resulted in hemiacetal **3a-Me** (*S*-configuration), which was isolated as a single diastereomer with OH and Ph groups in the *trans*-position (according to

Table 1 Screening of the Catalyst and the Solvent[a]



Entry	Solvent	Catalyst **4** (mol%)	Product **3a-Me**	
			Yield (%)	ee (%)
1	toluene	**4a** (10)	35	96
2	CH_2Cl_2	**4a** (10)	75	95
3	$CHCl_3$	**4a** (10)	70	95
4	THF	**4a** (10)	63	98
5	CH_2Cl_2	**4b** (5)	66	95
6	CH_2Cl_2	**4c** (5)	89	96[b]

[a] Conditions: **1** (0.24 mmol), **2a-Me** (0.2 mmol), catalyst **4** (5 and 10 mol%); r.t., 15 min; isolated yield after column chromatography; ee determined by HPLC analysis on a Chiralpak AS-H column. Always a single diastereoisomer was obtained.
[b] Formation of the opposite enantiomer was observed.



Scheme 1 The proposed reaction pathway

NMR spectra and X-ray crystal structure analysis, the absolute configuration according to X-ray crystal structure analysis). Dehydration product **7** was not detected.

Under the used conditions (catalyst **4c**, 5 mol%; α,β-unsaturated methyl keto ester **2a-Me**, CH_2Cl_2, r.t., 15 min,), the scope of the cascade reaction of cyclopentane-1,2-dione (**1**) with substituted (*E*)-2-oxobut-3-enoates **2** was investigated. The obtained results are presented in Scheme 2. Always the formation of single diastereoisomers was observed.

The electronic properties of the aromatic ring of α,β-unsaturated keto esters **2** did not influence the reaction: both **2e** (with an electron-donating group) and **2f** (with an electron-withdrawing group) reacted smoothly and afforded similar stereoselectivies. In addition, heteroaromatic thiophene substituted **2g** afforded the hemiacetal **3g** in slightly lower yield, but with good stereoselectivity. The change of methyl ester **2a-Me** to the more bulkier ethyl **2a-Et** and isopropyl ester **2a-*i*Pr** slightly decreased the yield and enantioselectivity of the reaction. It is noteworthy that alicyclic β-unsaturated-α-keto ester **2h** also afforded the addition-cyclization product **3h** with good enantioselectivity, although in slightly lower yield. 3-Substituted cyclopentane-1,2-diones gave unsuccessful results in the reaction with (*E*)-2-oxobut-3-enoates.

A special case was the 2-Cl-substituted hemiacetal **3d** (Scheme 2). In the NMR spectra, a hindered rotation of the singly 2-chloro-substituted phenyl ring around the substituted pyran ring was observed and a dynamic equilibrium between the two conformers exists. This phenomenon is best illustrated by the temperature dependence of the NMR spectra of the compound **3d**. In Figure 1, the fragments from ^1H and ^{13}C spectra of **3d** at room temperature and at –20 °C are presented.

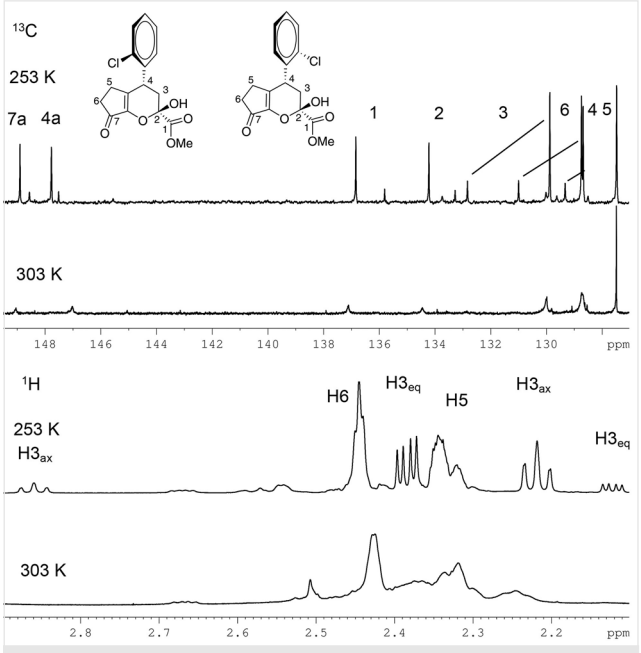
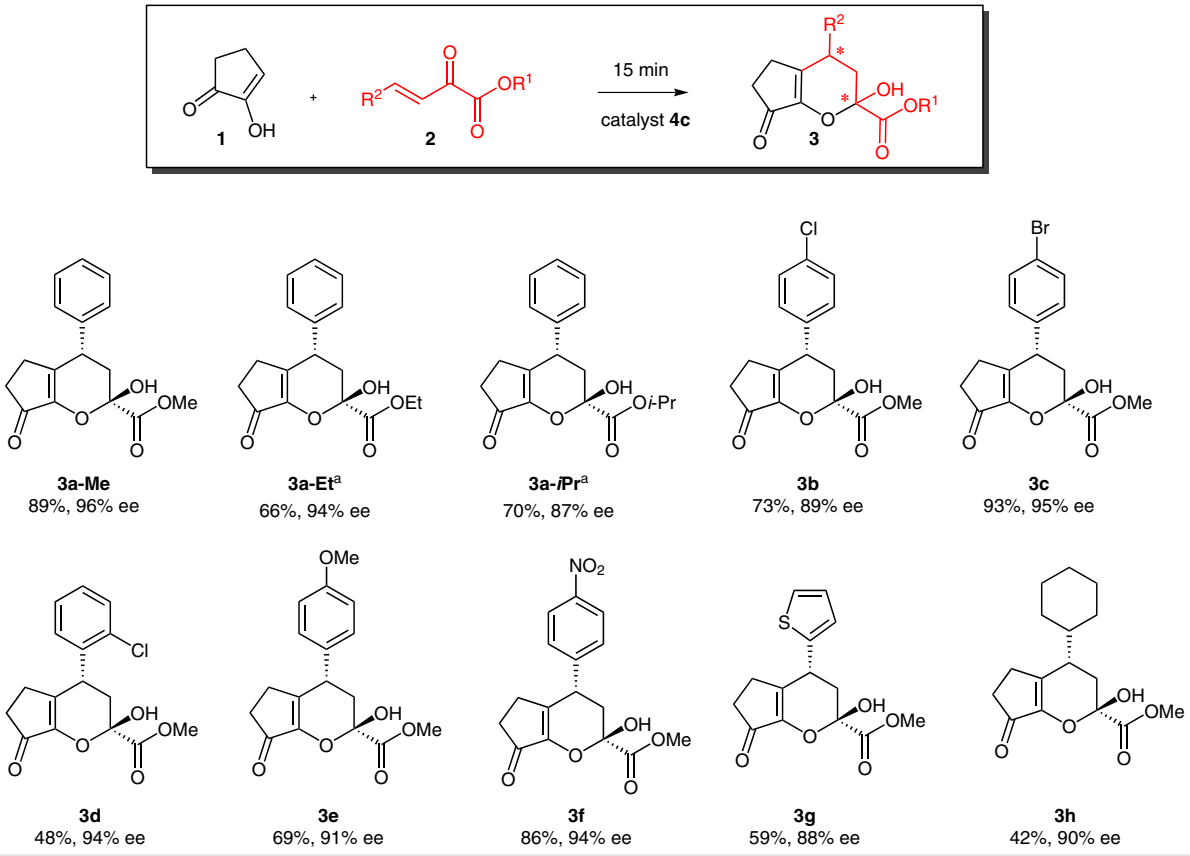


Figure 1 Fragments from ^{13}C and ^1H NMR spectra of compound **3d** at 303 and 253 K, showing the rotational isomers of the 2-Cl-substituted phenyl ring



Scheme 2 Scope of the reaction. All yields are isolated yields after column chromatography; all ee values were determined by HPLC on a Chiralpak AS-H column. [a] Reaction time 1 h.

The spectra of **3d** single diastereomer and the temperature dependence of the isomeric ratio point to atropisomerism with a comparatively low energy interconversion barrier between unequally populated rotational isomers. Atropisomers are usually defined with a half-life of at least 1000 seconds at 300 K.[24,25] In the present case, the room temperature half-life of **3d** is in millisecond range, with an atropisomer ratio of 5 to 1, the main isomer being *P* (a*R*, axially Rectus, plus) with the chlorine atom pointing towards the OH group (Figure 1). The assignment of the *P* configuration of the main isomer is based on the large downfield shift of H-3_{ax} from the inductive effect of chlorine in the minor isomer, the strongest NOE effect being from H-6 of the main isomer to H-3_{ax} and on the AM1 calculations of the optimized geometry of the *P* and *M* (a*S*, axially Sinister, minus) conformers of **3d** with an Arguslab 4.0.1[26] program. In both the *P* and *M* conformers, the calculated dihedral angle between C2*C1*C4H4 for optimized geometry was close to zero degree, which is also close to that obtained from X-ray data for compound **3b** (Figure 2, 3.5°). The *P*-isomer was calculated to be more stable by 1.1 kcal/mol, which should be compared with the experimental value from the 5 to 1 ratio of the isomers, giving a 0.95 kcal/mol energy difference for the conformers.

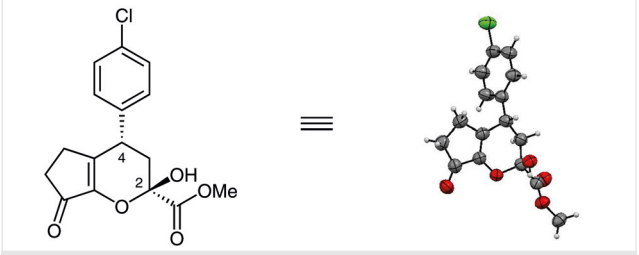
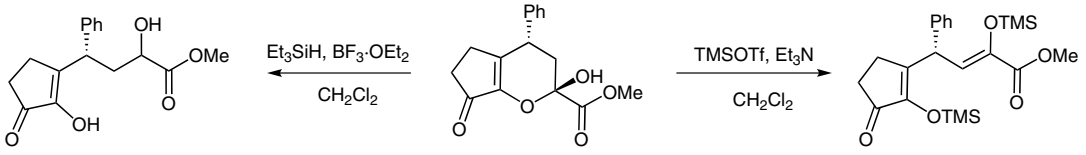


Figure 2 X-ray crystal structure of compound **3b**

The absolute configuration of the product **3b** was determined by an X-ray single crystal structure analysis to be 2*R*,4*S*. The absolute configurations of the other obtained compounds were proposed by analogy with the crystal structure (Figure 2).

By reducing bicyclic product **3a-Me** with Et_3SiH in the presence of Lewis acid, the monocyclic product **8** was obtained (Scheme 3). The keto group in the keto ester moiety



8
47%, 97% ee, 4:1 dr

3a-Me
96% ee

9
71%, 93% ee

Scheme 3 Transformation of hemiacetal **3a-Me** to substituted cyclopentane-1,2-dione derivatives

was reduced to an alcohol group. Two diastereoisomers were obtained in a 4 to 1 ratio with the prevailing thermodynamically more stable *trans*-isomer.

Furthermore, bicyclic product **3a-Me** when treated with an excess of silylating agent TMSOTf and Et_3N gave a disilylated dienol **9** (Scheme 3). The compounds **8** and **9** are valuable starting materials for further derivatizations, for example, for asymmetric oxidation, resulting in lactone carboxylic acids.[27]

Full assignments of the ^1H and ^{13}C chemical shifts are based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 and 800 MHz instruments. The residual solvent peaks ($CHCl_3/CDCl_3$, δ = 7.26/77.2) or TMS (TMS, δ = 0.00) were used as the chemical shift references. The chiral HPLC was performed using a Chiralpak AS-H column. The mass spectra were recorded on Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. The optical rotations were measured using an Anton Paar GWB Polarimeter MCP 500. The IR spectra were recorded on a Bruker Tensor 27 Fourier transform IR spectrophotometer. The absolute structure of a single crystal was obtained with a Rigaku Saturn944+ diffractometer. The Merck precoated silica gel 60 F_{254} plates were used for TLC, whereas for column chromatography the Merck 60 (0.040–0.063 mm) mesh silica gel was used. The commercial reagents and solvents were generally used as received.

Cyclopentane-1,2-dione (**1**) was prepared according to literature procedure[28] from commercially available cyclopentanone. γ-Aryl-β,γ-unsaturated-α-keto esters **2a**–**g** were prepared according to literature procedure[29] from the corresponding commercially available carbaldehydes and pyruvic acid. γ-Alkyl-β,γ-unsaturated-α-keto ester **2h** was prepared also according to the literature procedure[30] from the corresponding carbaldehyde and methyl pyruvate.

Thiourea catalysts **4a**,[31] **4c**,[32] and squaramide catalyst **4b**[33] were prepared according to the literature procedures.

4-Substituted Methyl 2-Hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylates; Methyl (2*R*,4*S*)-2-Hydroxy-7-oxo-4-phenyl-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3a-Me); Typical Procedure

2-Hydroxycyclopent-2-enone (**1**; 23.5 mg, 0.24 mmol), keto ester **2a** (38.0 mg, 0.2 mmol), and the organocatalyst **4c** (4.1 mg, 0.01 mmol) were dissolved in CH_2Cl_2 (0.7 mL). The mixture was stirred at r.t. until completion of the reaction (TLC monitoring, eluent: CH_2Cl_2–EtOAc, 25:1). The mixture was purified by column chromatography (CH_2Cl_2–EtOAc, 25:1) to afford **3a-Me** as a white solid; yield: 51 mg (89%); mp 124–126 °C; $[\alpha]_D^{25}$ +152.4 (*c* 0.05, MeOH); 96% ee [deteremined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (9:1), 1 mL/min, 254 nm; t_R (major) = 37.7 min, t_R (minor) = 62.7 min].

IR (KBr): 3244, 2981, 1753, 1696, 1646, 1455, 1288, 1140, 1113, 1016, 703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.20 (m, 5 H), 4.83 (s, 1 H), 3.98 (ddm, *J* = 11.9, 6.8 Hz, 1 H), 3.86 (s, 3 H), 2.42–2.24 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.7, 169.3, 148.4, 148.2, 139.5, 129.1, 128.2, 127.6, 95.6, 53.6, 38.4, 36.1, 32.8, 23.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{16}O_5]^+$: 289.1071; found: 289.1071.

Ethyl (2*R*,4*S*)-2-Hydroxy-7-oxo-4-phenyl-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3a-Et)

Yield: 40 mg (66%); colorless oil; $[\alpha]_D^{25}$ +139.3 (*c* 0.04, MeOH); 94% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 9.8 min, t_R (minor) = 18.7 min].

IR (film): 3392, 2983, 1748, 1712, 1648, 1495, 1454, 1228, 1137, 1110, 1024, 844, 755 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.21 (m, 5 H), 4.72 (d, *J* = 1.7 Hz, 1 H), 4.38–4.24 (m, 2 H), 3.97 (ddm, *J* = 11.9, 6.6 Hz, 1 H), 2.43–2.24 (m, 6 H), 1.33 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.4, 168.9, 148.5, 148.0, 139.6, 129.1, 128.3, 127.6, 95.5, 63.3, 38.5, 36.2, 32.8, 23.3, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{17}H_{18}O_5]$: 303.1227; found: 303.1231.

Isopropyl (2*R*,4*S*)-2-Hydroxy-7-oxo-4-phenyl-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3a-*i*-Pr)

Yield: 44 mg (70%); white solid; mp 55–56 °C; $[\alpha]_D^{25}$ +130.5 (*c* 0.04, MeOH); 87% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 7.5 min, t_R (minor) = 11.8 min].

IR (KBr): 3229, 2983, 1741, 1699, 1643, 1495, 1405, 1246, 1179, 1099, 846, 767 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 5 H), 5.12 (hept, *J* = 6.3 Hz, 1 H), 4.70 (d, *J* = 1.9 Hz, 1 H), 3.99–3.91 (m, 1 H), 2.43–2.23 (m, 6 H), 1.29 and 1.33 (2 d, *J* = 6.3 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.8, 166.6, 146.8, 146.2, 137.9, 127.3, 126.5, 125.7, 93.6, 69.8, 36.8, 34.4, 31.0, 21.4, 19.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{18}H_{20}O_5]^+$: 317.1384; found: 317.1384.

Methyl (2*R*,4*S*)-4-(4-Chlorophenyl)-2-hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3b)

Yield: 47 mg (73%); white solid; mp 141–142 °C; $[\alpha]_D^{25}$ +186.0 (*c* 0.04, MeOH); 89% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 20.1 min, t_R (minor) = 29.5 min].

IR (KBr): 3400, 2955, 1753, 1708, 1648, 1492, 1381, 1244, 1180, 1111, 1015, 845, 818 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 2 H), 7.20–7.15 (m, 2 H), 4.77 (s, 1 H), 3.96 (ddm, *J* = 11.9, 6.9 Hz, 1 H), 3.87 (s, 3 H), 2.44–2.21 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.4, 169.1, 148.5, 147.1, 138.0, 133.4, 129.6, 129.3, 95.5, 53.7, 37.9, 36.0, 32.7, 23.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{15}ClO_5]^+$: 323.0681; found: 323.0681.

Methyl (2*R*,4*S*)-4-(4-Bromophenyl)-2-hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3c)

Yield: 68 mg (93%); white solid; mp 140–142 °C; $[\alpha]_D^{25}$ +119.5 (*c* 0.05, MeOH); 95% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 19.5 min, t_R (minor) = 30.8 min].

IR (KBr): 3400, 2954, 1753, 1708, 1648, 1489, 1283, 1244, 1179, 1112, 1073, 1010, 904, 818 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.49 (m, 2 H), 7.14–7.09 (m, 2 H), 4.68 (s, 1 H), 3.94 (ddm, *J* = 11.9, 6.9 Hz, 1 H), 3.87 (s, 3 H), 2.43–2.21 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.4, 169.1, 148.5, 146.9, 138.5, 132.3, 130.0, 121.5, 95.5, 53.7, 38.0, 36.0, 32.7, 23.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{15}BrO_5]^+$: 367.0176; found: 367.0174.

Methyl (2*R*,4*R*)-4-(2-Chlorophenyl)-2-hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3d)

Yield: 31 mg (48%); white solid; mp 65–66 °C; $[\alpha]_D^{25}$ +82.3 (*c* 0.04, MeOH); 94% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 16.8 min, t_R (minor) = 40.0 min].

IR (KBr): 3400, 2955, 1754, 1710, 1648, 1440, 1284, 1229, 1180, 1112, 1077, 1036, 904, 758 cm^{-1}.

2*R*,4*R*-Isomer (major, *P*-configuration)

^1H NMR (800 MHz, $CDCl_3$, 253 K): δ = 7.42 (dd, *J* = 8.0, 1.0 Hz, 1 H, H-3*), 7.29 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1 H, H-5*), 7.24 (td, *J* = 8.0, 1.5 Hz, 1 H, H-4*), 7.13 (dd, *J* = 7.5, 1.5 Hz, 1 H, H-6*), 5.11 (d, *J* = 1.3 Hz, 1 H, OH), 4.63 (dd, *J* = 12.2, 6.1 Hz, 1 H, H-4), 3.84 (s, 3 H, OCH_3), 2.44 (m, 2 H, H-6), 2.37 (dd, *J* = 13.6, 6.1 Hz, 1 H, H-3*eq*), 2.32 (m, 2 H, H-5), 2.21 (ddd, *J* = 13.6, 12.2, 1.3 Hz, 1 H, H-3*ax*); * refers to the numbering of the aromatic ring.

^{13}C NMR (201 MHz, $CDCl_3$, 253 K): δ = 201.3 (C-7), 169.2 (CO_2), 149.1 (C-7a), 147.9 (C-4a), 137.0 (C-1*), 134.4 (C-2*), 130.0 (C-3*), 128.9 (C-6*), 128.8 (C-4*), 127.6 (C-5*), 95.6 (C-2), 54.0 (OCH_3), 35.1 (C-3), 34.5 (C-4), 32.7 (C-6), 23.2 C-5); * refers to the numbering of the aromatic ring.

2*R*,4*R*-Isomer (minor, *M*-configuration)

^1H NMR (800 MHz, $CDCl_3$, 253 K): δ = 7.36 (br m, 1 H, H-6*), 7.34 (br m, 1 H, H-3*), 7.29 (br m, 2 H, H-4*, H-5*), 5.09 (d, *J* = 1.3 Hz, 1 H, OH), 4.35 (br m, 1 H, H-4), 3.85 (s, 3 H, OCH_3), 2.85 (br t, *J* = 2 × 12.5 Hz, 1 H, H-3*ax*), 2.44 (m, 2 H, H-6), 2.32 (m, 2 H, H-5), 2.11 (dd, *J* = 13.5, 5.8 Hz, 1 H, H-3*eq*); * refers to the numbering of the aromatic ring.

^{13}C NMR (201 MHz, $CDCl_3$, 253 K): δ = 201.2 (C-7), 169.4 (CO_2), 148.7 (C-7a), 147.7 (C-4a), 136.0 (C-1*), 133.4 (C-2*), 133.0 (C-3*), 131.2 (C-6*), 129.5 (C-4*), 127.6 (C-5*), 95.5 (C-2), 54.0 (OCH_3), 39.7 (C-4), 32.8 (C-6), 32.0 (C-3), 23.8 C-5); * refers to the numbering of the aromatic ring.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{15}ClO_5]^+$: 323.0681; found: 323.0678.

Methyl (2*R*,4*R*)-2-Hydroxy-4-(4-methoxyphenyl)-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3e)

Yield: 44 mg (69%); white solid; mp 64–66 °C; $[\alpha]_D^{25}$ +162.2 (*c* 0.04, MeOH); 91% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 25.3 min, t_R (minor) = 53.9 min].

IR (KBr): 3398, 2955, 1753, 1708, 1646, 1513, 1442, 1253, 1179, 1110, 1077, 1030, 838, 819 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.12 (m, 2 H), 6.93–6.88 (m, 2 H), 4.64 (d, *J* = 1.7 Hz, 1 H), 3.92 (dd, *J* = 11.7, 6.6 Hz, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 2.41–2.24 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.6, 169.3, 159.0, 148.6, 148.2, 131.4, 129.2, 114.4, 95.6, 55.3, 53.7, 37.6, 36.2, 32.8, 23.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{17}H_{18}O_6]^+$: 319.1176; found: 319.1176.

Methyl (2*R*,4*S*)-2-Hydroxy-4-(4-nitrophenyl)-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3f)

Yield: 57 mg (86%); white solid; mp 145–146 °C; $[\alpha]_D^{25}$ +137.2 (*c* 0.04, MeOH); 94% ee [determined by HPLC on Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 52.3 min, t_R (minor) = 84.2 min].

IR (KBr): 3307, 2958, 1758, 1707, 1644, 1521, 1439, 1346, 1142, 1116, 980, 865, 722 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.23 (m, 2 H), 7.46–7.41 (m, 2 H), 4.74 (s, 1 H), 4.12 (t, *J* = 9.2 Hz, 1 H), 3.88 (s, 3 H), 2.46–2.20 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.1, 168.8, 148.8, 147.5, 147.1, 145.1, 129.2, 124.4, 95.3, 53.8, 38.4, 35.8, 32.7, 23.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{15}NO_7]^+$: 334.0921; found: 334.0919.

Methyl (2*R*,4*S*)-2-Hydroxy-7-oxo-4-(thiophen-2-yl)-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3g)

Yield: 35 mg (59%); white solid; mp 132–133 °C; $[\alpha]_D^{25}$ +122.8 (*c* 0.04, MeOH); 88% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 26.4 min, t_R (minor) = 45.1 min].

IR (KBr): 3243, 2951, 1751, 1696, 1647, 1436, 1296, 1108, 1013, 706 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 1 H), 7.03–6.96 (m, 2 H), 4.75 (d, *J* = 1.3 Hz, 1 H), 4.34 (dd, *J* = 10.5, 7.9 Hz, 1 H), 3.88 (s, 3 H), 2.46–2.31 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.5, 169.1, 147.5, 147.2, 141.9, 127.1, 125.9, 124.7, 95.6, 53.8, 36.3, 33.6, 32.7, 23.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{14}H_{14}O_5S]^+$: 295.0635; found: 295.0634.

Methyl (2*R*,4*S*)-4-Cyclohexyl-2-hydroxy-7-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-2-carboxylate (3h)

Yield: 25 mg (42%); white solid; mp 114 °C; $[\alpha]_D^{25}$ +49.5 (*c* 0.05, MeOH); 90% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 15.2 min, t_R (minor) = 21.3 min].

IR (KBr): 3231, 2925, 2851, 1738, 1689, 1643, 1439, 1290, 1113, 1003, 831 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.54 (s, 1 H), 3.86 (s, 3 H), 2.80–2.72 (m, 1 H), 2.58–2.41 (m, 4 H), 2.04 (dt, *J* = 13.7, 6.3 Hz, 1 H), 1.95 (dd, *J* = 13.4, 6.2 Hz, 1 H), 1.87–1.62 (m, 5 H), 1.38–1.04 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.5, 169.7, 149.7, 148.6, 95.8, 53.6, 38.6, 36.5, 32.8, 31.0, 28.2, 28.0, 26.8, 26.6, 26.4, 23.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{22}O_5]^+$: 295.1540; found: 295.1539.

Methyl 2-Hydroxy-4-(2-hydroxy-3-oxocyclopent-1-en-1-yl)-4-phenylbutanoate (8)

According to a modified literature procedure,[34] hexahydrocyclopenta[*b*]pyran-2-carboxylate **3a-Me** (80 mg, 0.28 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). Et_3SiH (49 mg, 0.42 mmol) and $BF_3{\cdot}OEt_2$ (45 mg, 0.32 mmol) were added under dry argon flow at –76 °C. The mixture was warmed to 0 °C over 4 h and stirred overnight at 0 °C. The reaction was quenched with H_2O (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined and dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by column chromatography (CH_2Cl_2–EtOAc, 5:1) to afford the product as a transparent oil; yield: 38 mg (47%); colorless oil; $[\alpha]_D^{25}$ –6.8 (*c* 0.04, MeOH); 97% ee [determined by HPLC: Chiralpak AS-H; hexane–*i*-PrOH (8:2), 1 mL/min, 254 nm; t_R (major) = 22.7 min, t_R (minor) = 30.8 min].

IR (film): 3356, 2954, 1695, 1651, 1601, 1495, 1441, 1391, 1225, 1102, 913, 732, 703 cm^{-1}.

Ratio of 2*S*/2*R* = 4:1. In the most stable conformation, the chain from C-1 to phenyl ring is *trans* oriented. In this conformation, H-2 and H-4 from *S*,*S*-isomer are low-field shifted from the OH group of the five-membered ring and from the 2-OH, correspondingly. The 2*S*,4*S*-isomer is, according to AM1 calculations, more stable by 0.56 kcal/mol.

2*S*,4*S*-Isomer (major)

^{1}H NMR (800 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 4 H, C_6H_5 H-*o*,*m*), 7.21–7.19 (m, 1 H, C_6H_5 H-*p*), 6.14 (br s, 1 H, enol OH), 4.19 (dd, *J* = 10.4, 5.5 Hz, 1 H, H-4), 4.15 (dd, *J* = 9.3, 3.7 Hz, 1 H, H-2), 3.65 (s, 3 H, OCH_3), 3.06 (br s, 1 H, 2-OH), 2.68 (ddd, *J* = 13.9, 10.4, 3.7 Hz, 1 H, H-3), 2.39 (m, 1 H, H-5*), 2.32 (m, 2 H, H-4*), 2.27 (m, 1 H, H-5*), 2.15 (ddd, *J* = 13.9, 9.3, 5.5 Hz, 1 H, H-3); * refers to the numbering of cyclopentenyl ring.

^{13}C NMR (201 MHz, $CDCl_3$): δ = 203.7 (C-3*), 175.4 (CO_2), 148.8 (C-2*), 146.9 (C-1*), 141.4 (C-*i*), 128.9 (C-*m*), 128.2 (C-*o*), 127.3 (C-*p*), 68.9 (C-2), 52.8 (OCH_3), 41.6 (C-4), 37.0 (C-3), 31.9 (C-4*), 23.8 C-5*); * refers to the numbering of cyclopentenyl ring.

2*R*,4*S*-Isomer (minor)

^{1}H NMR (800 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 4 H, C_6H_5 H-*o*,*m*), 7.21–7.19 (m, 1 H, C_6H_5 H-*p*), 6.07 (br s, 1 H, enol OH), 4.19 (dd, *J* = 9.9, 5.8 Hz, 1 H, H-4), 4.15 (dd, *J* = 9.6, 3.5 Hz, 1 H, H-2), 3.70 (s, 3 H, OCH_3), 2.91 (br s, 1 H, 2-OH), 2.57 (ddd, *J* = 14.0, 9.9, 3.5 Hz, 1 H, H-3), 2.39 (m, 1 H, H-5*), 2.32 (m, 2 H, H-4*), 2.27 (m, 1 H, H-5*), 2.26 (ddd, *J* = 14.0, 9.6, 5.9 Hz, 1 H, H-3); * refers to the numbering of cyclopentenyl ring.

^{13}C NMR (201 MHz, $CDCl_3$): δ = 203.9 (C-3*), 175.7 (CO_2), 148.3 (C-2*), 147.7 (C-1*), 140.5 (C-*i*), 129.0 (C-*m*), 128.4 (C-*o*), 127.4 (C-*p*), 68.5 (C-2), 52.8 (OCH_3), 42.2 (C-4), 37.0 (C-3), 31.8 (C-4*), 24.1 C-5*); * refers to the numbering of cyclopentenyl ring.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{16}H_{18}O_5]^+$: 291.1188; found: 291.1228.

Methyl (*Z*)-4-{3-Oxo-2-[(trimethylsilyl)oxy]cyclopent-1-en-1-yl}-4-phenyl-2-[(trimethylsilyl)oxy]but-2-enoate (9)

According to a modified literature procedure,[35] hexahydrocyclopenta[*b*]pyran-2-carboxylate **3a-Me** (50 mg, 0.17 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). Et_3N (45 mg, 0.53 mmol) and TMSOTf (118 mg, 0.53 mmol) were added, respectively, to the mixture at 0 °C. The reaction mixture was stirred at r.t. until the end of reaction (TLC monitoring, eluent: CH_2Cl_2–EtOAc, 10:1). The reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined and dried (Na_2SO_4). CH_2Cl_2 was evaporated and the crude product was purified by column chromatography (CH_2Cl_2–EtOAc 40:1) to give **9** as a transparent oil; yield: 53 mg (71%); colorless oil; $[\alpha]_D^{25}$ –12.3 (*c* 0.04, MeOH); 93% ee [determined by HPLC: Chiralpak OD-H; hexane–*i*-PrOH (99:1), 1 mL/min, 254 nm; t_R (major) = 5.3 min, t_R (minor) = 5.7 min].

IR (film): 2956, 1728, 1712, 1643, 1494, 1439, 1498, 1252, 1139, 1112, 872, 849, 758, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 5 H), 6.50 (d, *J* = 9.9 Hz, 1 H), 5.12 (d, *J* = 9.9 Hz, 1 H), 3.78 (s, 3 H), 2.53–2.44 (m, 1 H), 2.39–2.29 (m, 3 H), 0.25–0.23 (m, 9 H), 0.18–0.15 (m, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.4, 165.2, 153.0, 149.2, 141.3, 140.9, 128.9, 127.7, 127.0, 120.2, 52.2, 41.2, 32.2, 23.0, 1.2, 0.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{22}H_{32}O_5Si_2]^+$: 433.1822; found: 433.1855.

Acknowledgment

The authors thank the Estonian Ministry of Education and Research (Grants No. IUT 19-32, IUT 19-9 and IUT 23-7) and EU European Regional Development Fund (3.2.0101.08-0017) for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560347.

References

(1) (a) Rueping, M.; Merino, E.; Sugiono, E. *Adv. Synth. Catal.* **2008**, *350*, 2127. (b) Rueping, M.; Sugiono, E.; Merino, E. *Chem. Eur. J.* **2008**, *14*, 6329. (c) Franke, P. T.; Richter, B.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 6317.

(2) (a) Krishnakumar, V.; Mandal, B. K.; Khan, F.-R. N.; Jeong, E. D. *Tetrahedron Lett.* **2014**, *55*, 3717. (b) Ren, Q.; Sun, S.; Huang, J.; Li, W.; Wu, M.; Guo, H.; Wang, J. *Chem. Commun.* **2014**, *50*, 6137. (c) Rao, L. C.; Meshram, H. M.; Kumar, N. S.; Rao, N. N.; Babu, N. J. *Tetrahedron Lett.* **2014**, *55*, 1127.
(3) Nair, D. K.; Menna-Barreto, R. F. S.; Silva Junior, E. N.; Mobin, S. M.; Namboothiri, N. N. *Chem. Commun.* **2014**, *50*, 6973.
(4) Urbanietz, G.; Atodiresei, I.; Enders, D. *Synthesis* **2014**, *46*, 1261.
(5) Moghaddam, F. M.; Mirjafary, Z.; Javan, M. J.; Motamen, S.; Saeidian, H. *Tetrahedron Lett.* **2014**, *55*, 2908.
(6) Zhao, B.-L.; Du, D.-M. *Tetrahedron: Asymmetry* **2014**, *25*, 310.
(7) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 3699.
(8) (a) Rueping, M.; Kuenkel, A.; Fröhlich, R. *Chem. Eur. J.* **2010**, *16*, 4173. (b) Ding, D.; Zhao, C.-G.; Guo, Q.; Arman, H. *Tetrahedron* **2010**, *66*, 4423. (c) Li, W.; Liu, X.; Mao, Z.; Chen, Q.; Wang, R. *Org. Biomol. Chem.* **2012**, *10*, 4767.
(9) Ren, Q.; Gao, Y.; Wang, J. *Org. Biomol. Chem.* **2011**, *9*, 5297.
(10) (a) Lee, J. H.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2013**, *34*, 1619. (b) Song, X.; Liu, J.; Liu, M.-M.; Wang, X.; Zhang, Z.-F.; Wang, M.-C.; Chang, J. *Tetrahedron* **2014**, *70*, 5468. (c) Wang, Y.-F.; Wang, K.; Zhang, W.; Zhang, B.-B.; Zhang, C.-X.; Xu, D.-Q. *Eur. J. Org. Chem.* **2012**, 3691. (d) Chen, X.-K.; Zheng, C.-W.; Zhao, S.-L.; Chai, Z.; Yang, Y.-Q.; Zhao, G.; Cao, W.-G. *Adv. Synth. Catal.* **2010**, *352*, 1648.
(11) Preegel, G.; Noole, A.; Ilmarinen, K.; Järving, I.; Kanger, T.; Pehk, T.; Lopp, M. *Synthesis* **2014**, *46*, 2595.
(12) Reile, I.; Paju, A.; Kanger, T.; Järving, I.; Lopp, M. *Tetrahedron Lett.* **2012**, *53*, 1476.
(13) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2013**, *113*, 5924.
(14) Zhang, Y.; Liu, X.; Zhao, X.; Zhang, J.; Zhou, L.; Lin, L.; Feng, X. *Chem. Commun.* **2013**, *49*, 11311.
(15) Suh, C. W.; Han, T. H.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2013**, *34*, 1623.
(16) (a) Shen, J.; Liu, D.; An, Q.; Liu, Y.; Zhang, W. *Adv. Synth. Catal.* **2012**, *354*, 3311. (b) Shen, J.; An, Q.; Liu, D.; Liu, Y.; Zhang, W. *Chin. J. Chem.* **2012**, *30*, 2681.
(17) Lin, N.; Deng, Y.-Q.; Zhang, Z.-W.; Wang, Q.; Lu, G. *Tetrahedron: Asymmetry* **2014**, *25*, 650.
(18) Sinha, D.; Perera, S.; Zhao, J. C.-G. *Chem. Eur. J.* **2013**, *19*, 6976.
(19) Lv, J.; Zhong, X.; Cheng, J.-P.; Luo, S. *Acta Chim. Sinica* **2012**, *70*, 1518.
(20) Murugan, K.; Srimurugan, S.; Chen, C. *Chem. Commun.* **2010**, *46*, 1127.
(21) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312.
(22) (a) Ghosh, A. K. Patent WO2012/092168, **2012**. (b) Ghosh, A. K.; Chapsal, B. D.; Mitsuya, D. Patent US2013/0289067, **2013**.
(23) (a) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253. (b) Li, Y.; Li, X.; Cheng, J.-P. *Adv. Synth. Catal.* **2014**, *356*, 1172. (c) Diaz-de-Villegas, M. D.; Galvez, J. A.; Badorrey, R.; Lopez-Ram-de-Viu, P. *Adv. Synth. Catal.* **2014**, *356*, 3261.
(24) (a) M. Ōki further refined the definition of atropisomers taking into account the temperature-dependence associated with the interconversion of conformers, specifying that atropisomers interconvert with a half-life of at least 1000 seconds at a given temperature, corresponding to an energy barrier of 93 kJ mol^{-1} (22 kcal mol^{-1}) at 300 K (27 °C). (b) Oki, M. *Recent Advances in Atropisomerism, In Topics in Stereochemistry*; Vol. 14; Allinger, N. L.; Eliel, E. L.; Wilen, S. H., Eds.; Wiley: Hoboken, **1983**, 1–82.
(25) Alkorta, I.; Elguero, J.; Roussel, C.; Vanthuyne, N.; Piras, P. *Adv. Heterocycl. Chem.* **2012**, *105*, 1.
(26) Thompson, M. *ArgusLab 4.0.1* 2004.
(27) (a) Paju, A.; Kanger, T.; Pehk, T.; Lindmaa, R.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1565. (b) Paju, A.; Kanger, T.; Pehk, T.; Eek, M.; Lopp, M. *Tetrahedron* **2004**, *60*, 9081.
(28) Wrobel, J.; Cook, J. M. *Synth. Commun.* **1980**, *10*, 333.
(29) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714.
(30) Feng, J.; Fu, X.; Chen, Z.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2013**, *15*, 2640.
(31) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.
(32) Tomotaka, O.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.
(33) Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224.
(34) D'Oyley, J. M.; Aliev, A. E.; Sheppard, T. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 10747.
(35) Yamashita, D.; Murata, Y.; Hikage, N.; Takao, K.; Nakazaki, A.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 1404.