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Multicatalytic Enantioselective Borrowing Hydrogen δ-Lactonization Strategy from β-Keto Esters and Allylic Alcohols

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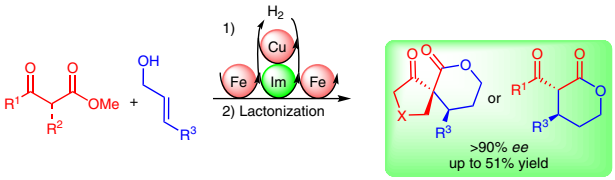

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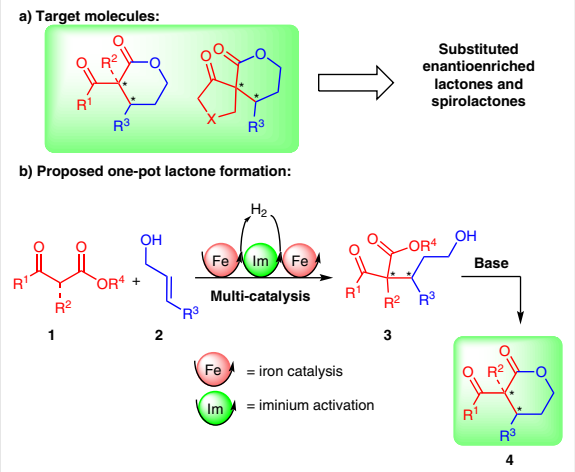
Abstract By combining an iron-catalyzed borrowing hydrogen of allylic alcohols with an enantioselective organocatalyzed Michael addition of β-keto esters followed by a subsequent DBU-promoted lactonization different enantioenriched δ-lactones have been synthesized with good enantioselectivities. The valuable building blocks, featuring in some cases challenging quaternary stereocenters, have been obtained with >90% *ee*.

Key words organocatalysis, iron catalysis, lactone synthesis, borrowing hydrogen, multi-catalysis

The ability of organic chemists to synthesize rapidly original scaffolds is crucial for the future development of the pharmaceutical industry. In this context, the control of the stereochemistry of the newly formed molecular entities while taking into account eco-compatibility parameters such as the minimization of steps, time, or waste is crucial. To fulfill the above mentioned goal, recent developments in the so-called 'borrowing hydrogen' reactions have considerably shortened existing routes and the associated waste generated to reach crucial building blocks.[1] In these reactions, a metal catalyst is able to reversibly activate in a transient manner molecules through hydrogen transfer allowing reactions on otherwise poorly reactive substrates. However, the challenge of the enantioselective construction of chiral molecules through such reversible hydrogen transfer has only received limited attention as compared to the corresponding racemic or achiral techniques.[2]

Substituted δ-lactones including spirocyclic congeners are common motifs represented in highly diversified families of natural products (Scheme 1, a).[3] Given the interesting biological profiles associated with these skeletons, organic chemists have been pushed to develop creative methods to access these scaffolds.[4] However, alternative methods decreasing time and waste for their preparation remain highly desirable to complete the toolbox available for synthetic chemists. We anticipated that a new enantioselective approach combining an iron-catalyzed borrowing hydrogen with an amino-catalyzed Michael addition should allow a rapid access to attractive δ-lactone frameworks (Scheme 1, b).[5] By allowing the condensation of appropriate β-keto esters **1** with allylic alcohols **2**, the resulting enantioenriched chiral alcohols **3** should then undergo a key cyclization affording the desired structures **4**.



Scheme 1 Proposed multi-catalytic approach towards enantioenriched δ-lactones

Our initial experiments conducted using a catalytic combination of iron cyclopentadienone complex **[Fe]**[6] and **Cat1**[7] to control the stereochemistry indicated that the key lactone precursors **3a–c** (2.3:1 ratio, equilibrium between

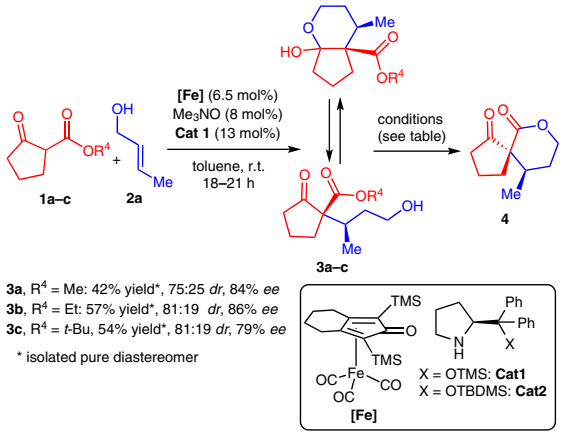
open form and lactol) could be prepared with 79 to 86% *ee* from readily available cyclic β-keto esters **1a–c** and crotyl alcohol (**2a**).[5a] In this reaction, the iron catalyst promotes a reversible hydrogen transfer from the alcohol to the aldehyde level while the organocatalyst controls the stereochemistry of the Michael addition on the formed α,β-unsaturated aldehyde.[8] From the obtained enantioenriched alcohols isolated as single diastereomers, several spirolactonization conditions were then tested (Table 1).[9] These investigations revealed the relative sensitivity of the obtained alcohols, particularly recalcitrant to the ring closure. From **3b**,**c** (R^4 = Et, *t*-Bu), using thermal (Table 1, entries 1, 4), acidic (entry 2), or mildly basic conditions (entry 3), only degradation of the starting material was observed possibly through side reaction of the unprotected ketone. Interestingly, when turning to the use of the less sterically hindered compound **3a** (R^4 = Me), using TBAF in THF afforded after one hour around 50% of the expected spirolactone **4** in combination with other undetermined side products (entry 7). Use of other bases such as Cs_2CO_3 or DBU in THF or toluene (entries 8, 9), resulted in better selectivity forming **4** in excellent 88–90% yield. Given the relative price of DBU versus Cs_2CO_3 we selected the conditions of entry 9 for the investigation of the scope of the lactonization.

Using the optimized conditions of Table 1, different cyclic keto esters and allylic alcohols combination were tested in the lactone formation (Scheme 2). Using aliphatic alcohols **2** (R^3 = Me, *n*-Pr, CH_2CH_2Ph), different spiro-δ-lactones **4–7** were formed in 25–37% yield over two steps with 73 to 90% *ee*. It is important to point out that the final lactones possessing a challenging quaternary stereocenter are isolated as single diastereomers, the minor one being separated by column chromatography after the first step of the process. Using the sterically hindered keto ester **1d** possessing a *gem*-dimethyl substituent, the reaction worked equally well forming **7** in 38% yield over two steps with 80% *ee*.

We recently reported that the addition of a soft Lewis acid such as $Cu(acac)_2$ could be beneficial to improve both reactivity and enantioselectivity in multi-catalyzed borrowing hydrogen.[10] We thus decided to verify the efficiency of a triple iron-, copper-, organocatalytic system towards spirolactone formation (Scheme 3). Gratifyingly, adding 5 mol% of $Cu(acac)_2$ to the system and performing the reaction at 10 °C, the first step worked better providing after DBU promoted lactonization, the expected spiro-δ-lactones with significantly improved *ee*. Using this two-step protocol, all spiro-δ-lactones were formed in ≥90% *ee* in 21 to 51% yield.

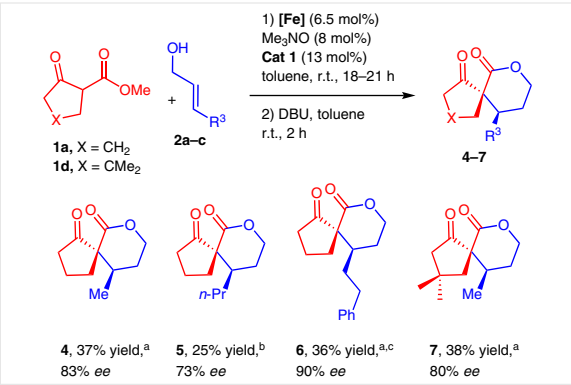
In order to simplify our approach, we subsequently wondered about applying a one-pot procedure where the intermediate lactol would not be isolated prior to spirolactonization limiting the number of operations necessary to access the key spirolactones. Interestingly, directly adding DBU after completion of the borrowing hydrogen, the expected lactone could be formed (Scheme 4). It is important to point out that a kinetic resolution of the intermediate lactol was observed here. Indeed, only the major diastereo-

Table 1 Selected Optimization for Spiro-δ-lactone **4** Formation

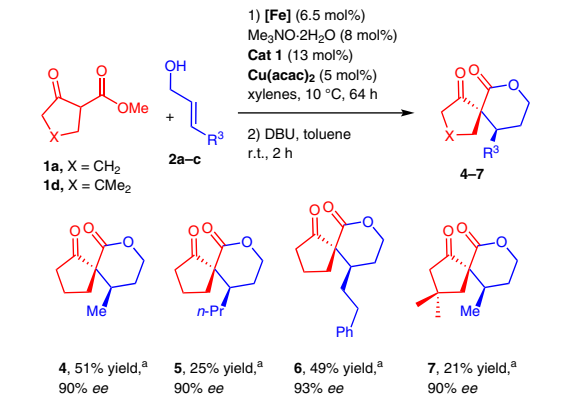


Entry	R^4 (**3**)	Lactonization conditions	Yield (%) of **4**
1	Et (**3b**)	toluene, 110 °C, 38 h	degradation
2	Et (**3b**)	PTSA, acetone, r.t., 8 h	degradation
3	Et (**3b**)	TBAF, THF, r.t., 1 h	degradation
4	*t*-Bu (**3c**)	toluene, 110 °C, 38 h	degradation
5	Me (**3a**)	NaH, THF, r.t., 8 h	degradation
6	Me (**3a**)	NaH, THF, r.t., 8 h	degradation
7	Me **(3a)**	TBAF, THF, 0 °C, 1 h	50%[a]
8	**Me (3a)**	**Cs_2CO_3, THF, r.t., 1 h**	**88[b]**
9	**Me (3a)**	**DBU, toluene, r.t., 2 h**	**90[b]**

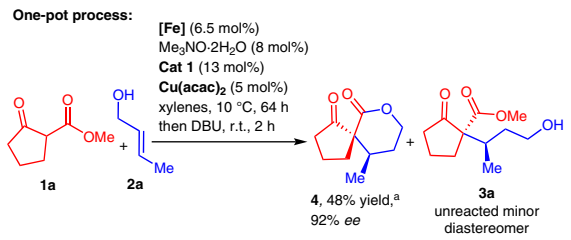
[a] Conversion as determined by ^1H NMR spectroscopy.
[b] Isolated yield.



Scheme 2 Scope of the bis-catalytic approach to enantioenriched spiro-δ-lactones **4–7**. [a] Isolated pure diastereomer. [b] *dr* = 85:15. [c] First step performed at 10 °C.



Scheme 3 Scope of the triple-catalytic approach to enenatioenriched spiro-δ-lactones **4–7**. [a] Isolated pure diastereoisomer.



Scheme 4 One-pot synthesis of spiro-δ-lactone **4**. [a] Isolated pure diastereomer.

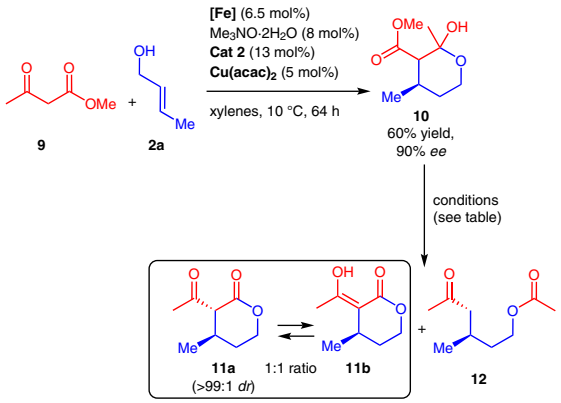
mer of intermediate **3a** reacted forming **4** in 48% yield and 92% *ee* while the minor diastereomer **3a** remained untouched.

Besides from spirolactones, we also wondered about the formation of simple stereodefined monocyclic lactones **11** starting from more challenging acyclic non-substituted β-keto esters such as methyl acetoacetate (**9**) (Table 2).[11] In this case, other possible reactivity issues at various stages of the sequence could replace the difficulty associated with the formation of a quaternary stereocenter. Indeed, the potential formation of a unproductive Knoevenagel adduct can inhibit the overall transformation, while the possible evolution of the transient Michael adduct **10** by a competitive retro-Dieckmann type fragmentation can produce the undesired acyclic ketone **12**.[5b] However, gratifyingly the triple-catalytic enantioselective sequence proved to be efficient with **9** and crotyl alcohol (**2a**) leading to the expected reduced Michael adduct **10** as its hemiacetal form in 60% yield and 90% *ee*.

From here, initial lactonization attempt using the same conditions as for spirolactones (Table 2) failed and virtually no conversion of **10** was observed (Table 2, entry 1). When forcing the conditions by increasing the temperature to 60 or 80 °C (entries 2, 3), a partial conversion, a mixture of δ-lactones **11a**,**b** and fragmentation product **12** was observed. It is important to notice that the expected lactone is in equilibrium between the ketone **11a** (99:1 *dr*) and the enol **11b**. By increasing the reaction time (48 h at 80 °C, entry 4), the reaction mixture converged to the formation of the fragmentation product **12**. In order to push the reactivity to the sole formation of the lactone, we next turned our attention to the use of microwave activation in order to shorten the required reaction time and potentially push the conversion while limiting the formation of the thermodynamic product **12**.

Heating **10** at 60 °C under microwave activation avoided the formation of the fragmentation product with a conversion of 20% after 10 minutes of heating (entry 5). Increasing the temperature to 80 or 100 °C (entries 6, 7), increased the conversion still avoiding the formation of **12**. Unfortunately, decomposition of **11** also occurred at these temperatures limiting the isolated yields to 28–30%. Finally, we found that gently heating at 60 °C under microwave irradiation for 120 minutes afforded the best compromise between conversion and decomposition allowing the isolation of **11** in 54% yield (71% based on recovered starting material).

Table 2 Selected Optimization for Formation of δ-Lactones **11**



Entry	Lactonization conditions	Ratio[a] **10**/**11**/**12**	Yield (%)[b] of **11**
1	DBU, toluene, r.t., 2 h	99:1:1	–
2	DBU, toluene, 60 °C, 12 h	76:99:1	nd
3	DBU, toluene, 80 °C, 14 h	1.3:1:1.6	nd
4	DBU, toluene, 80 °C, 48 h	1.2:1:5.4	nd
5	DBU, toluene, 60 °C, MW, 10 min	99:24:1	nd
6	DBU, toluene, 80 °C, MW, 90 min	40:99:1	28
7	DBU, toluene, 100 °C, MW, 20 min	32:99:1	30
8	**DBU, toluene, 60 °C, MW, 30 min**	**52:99:1**	**52 (71, brsm)**

[a] Determined by ^{1}H NMR spectroscopy.
[b] Isolated yield; nd = not determined.

In conclusion, we have shown that combining a cooperative multiple catalytic enantioselective sequence with a DBU-promoted lactonization allowed the formation of valuable δ-lactones starting from simple β-keto esters and allylic alcohols. Thanks to the cooperative role of the different catalysts, these lactones were formed in >90% *ee*. In addition, spirolactones were synthesized with the controlled formation of challenging quaternary stereocenters.

Finally, this two-step sequence could be combined in one pot, reducing the required operations to access these building blocks, which should ensure a rapid application of this strategy.

NMR spectra were recorded on a Bruker AC 300 (300 MHz) or a Bruker AC 400 (400 MHz) spectrometer in $CDCl_3$. Chemical shifts are given in ppm, using as internal standards the residual $CHCl_3$ signal for ^1H NMR (δ = 7.26) and the deuterated solvent signal for ^{13}C NMR (δ = 77.0). Data for ^{13}C NMR are reported as follows: chemical shift (multiplicity). Data for ^1H NMR are reported as follows: chemical shift [multiplicity (standard abbreviations), coupling constant *J* in hertz (Hz), integration]. Anhyd toluene was obtained from a Solvent Purification System M Braun SPS-800. Unless specified, all other solvents were used in their commercial form without further purification. TLC analyses were conducted on Merck 60 F254 silica gel plates and on Alugram ALOX N/UV254 and revealed under UV lamp (λ = 254 nm) and with universal stain: *p*-anisaldehyde (prepared from 5 mL of *p*-anisaldehyde with 30 g of ice, 60 mL of EtOH, 5 mL of H_2SO_4, and 0.5 mL of AcOH). Flash Chromatography was performed following the method of Still on 40–63 µm silica gel or 63–200 µm Al_2O_3 90 active basic eluted with the specified eluent.

High-resolution mass spectra (HRMS) were performed on a QStar Elite (Applied Biosystems SCIEX) spectrometer equipped with pneumatically assisted atmospheric pressure ionization source (API). Samples were ionized by positive electrospray mode as follow: electrospray tension (ISV): 5500 V; opening tension (OR): 50 V; nebulization gas pressure (air): 20 psi.

Chiral HPLC analyses were performed at the Chiral Chromatography Laboratory of Aix Marseille University (iSm2, plateforme de Chromatographie Chirale et de Stéréochimie Dynamique). The screening of chiral stationary phases was performed on two chromatographic units: 1) Merck-Lachrom unit: Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7200 autosampler, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV-detector, with EZChrom Elite software. 2) Lachrom-Elite unit : L-2130 pump, L-2200 autosampler, L-2350 oven and DAD L-2455 detector. The samples were also detected by detectors of chirality: Jasco OR-1590 polarimeter or Jasco CD-1595 detector. Hexane, *i*-PrOH and EtOH, HPLC grade, from Hipersolv Chromanorm (VWR), were degassed and filtered on a 0.45 µm millipore membrane before use. Retention time (Rt, abbreviated as t_R in the experimental part) in min, retention factor ki = (Rti–Rt0)/Rt0 and enantioselectivity factor $\alpha = k_2/k_1$ are given. Rt0 was determined by injection of tri-*tert*-butylbenzene.

The different analytical columns (250 × 46 mm)® tested are Chiralcel OD-3, OJ-H, Chiralpak® AS-H, AD-H, AZ-H, IA, IB, and IC columns from Chiral Technology Europa (Illkirch, France), Lux-Amylose-2, Lux-Cellulose-2, and Lux-Cellulose-4, from Phenomenex and Whelk-O1 (*S*,*S*) and Ulmo (*S*,*S*) from Regis Technologies (Morton Grove, USA). Chiral GC analysis were performed on a HP 4890 using 6 bar argon as vector. Column: Hydrodex-β, Lipodex-e from Macherey-Nagel (25 m/0.25 mm) and Cyclosil-B from Agilent J & W (30 m/0.25 mm/0.25 µm). Chromatogram was analyzed with ChromNav software.

Optical rotations were measured at 25 °C in $CHCl_3$ with an Anton Paar MCP 200 polarimeter with a 0.2 cm length. HPLC/GC racemates were prepared by using a 1:1 *R* and *S* mixture of diaryl prolinol silyl ether catalyst **Cat1**. All commercially available reagents were used as received, except crotonaldehyde, which was distilled under argon before use.

Iron-, Organocatalytic Catalytic Enantioselective Borrowing Hydrogen; General Procedure (GP1)

To a solution of β-keto ester **1** (0.3 mmol, 1 equiv in anhyd toluene (0.9 mL) was successively added **Cat 1** (12.5 mg, 0.039 mmol, 13 mol%) and allylic alcohol **2** (0.45 mmol, 1.5 equiv). **[Fe]** complex (8.2 mg, 0.0195 mmol, 6.5 mol%) and Me_3NO (1.8 mg, 0.024 mmol, 8 mol%) were then added all at once. Argon was immediately passed through the vial for 20 seconds, the vial was closed, and the contents were stirred at r.t. (20–22 °C) for the indicated time. Sat. aq NH_4Cl (1.5 mL) was then added, the aqueous layer extracted with Et_2O (3 × 2 mL), the combined organic layers dried (Na_2SO_4), filtered, and the solvent evaporated. Purification over silica gel (PE/EtOAc, unless otherwise specified) afforded the expected functionalized alcohol in equilibrium between open and closed form.

Triple Catalytic Enantioselective Borrowing Hydrogen; General Procedure (GP2)

To a solution of β-keto ester **1** (0.2 mmol, 1 equiv) in anhyd xylenes (0.6 mL) were added successively, allylic alcohol **2** (0.4 mmol, 2 equiv), $Cu(acac)_2$ (2.4 mg, 0.01 mmol, 5 mol%), and **Cat1** (9.4 mg, 0.026 mmol, 13 mol%). **[Fe]** complex (5.4 mg, 0.013 mmol, 6.5 mol%) and $Me_3NO{\cdot}2H_2O$ (1.8 mg, 0.016 mmol, 8 mol%) were added all at once. Argon was immediately passed through the vial for 20 seconds, the vial was closed, and the contents were stirred at 10 °C for the indicated time. Sat. aq NH_4Cl (1.5 mL) was added and the aqueous layer extracted with Et_2O (3 × 2 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed under vacuum. Purification over silica gel (PE/EtOAc, unless otherwise specified) afforded the expected functionalized alcohol in equilibrium between open and closed forms.

Methyl (*R*)-1-[(*R*)-4-Hydroxybutan-2-yl]-2-oxocyclopentane-1-carboxylate (3a)

Prepared according to the general triple catalytic procedure (GP2) starting from β-keto ester **1a** (28.4 mg, 0.2 mmol) and allylic alcohol **2a** (28.8 mg, 0.4 mmol), and purified by chromatography over silica gel (PE/EtOAc 9:1 to 8:2). The product was isolated as a pale yellow oil with >95:5 *dr*; yield: 23 mg (55%, 0.101 mmol); 90% *ee*.

The product was obtained as a mixture of open A and closed B forms in a 2.3:1 ratio; R_f = 0.11 (PE/EtOAc, (7:3); $[\alpha]_D^{20}$ –9.3 ($CHCl_3$, *c* = 0.41, 84% *ee* sample).

HPLC determination of the enantiomeric excess on the corresponding benzoyl protected alcohol prepared according to procedure C as reported in our earlier work.[5] Lux-Amylose-2, hexane/EtOH (90:10), 1 mL/min, UV 220 nm: t_R (major) = 15.8 min, t_R (minor) = 23.8 min.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8 Hz, CH_3, A), 1.00 (d, *J* = 6.8 Hz, CH_3, B), 1.20–2.18 (m, 7 H, A + B + OH, A), 2.38–2.56 (m, 2 H, A + B), 3.50–3.73 (m, 4 H, A + B + 1 H of CH_2, B), 4.08 (ddd, *J* = 4.4, 3.6, 3.4 Hz, 1 H of CH_2, B), 4.26 (br s, OH, B).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (CH_3, A), 16.9 (CH_3, B), 18.1 (CH_2, B), 19.7 (CH_2, A), 28.0 (CH_2, A), 31.8 (CH_2, B), 31.9 (CH, B), 33.4 (CH, A), 35.9 (CH_2, B), 39.0 (CH_2, A), 51.7 (CH_3, B), 52.7 (CH_3, A), 56.7 (Cquat, B), 59.3 (CH_2, B), 60.7 (CH_2, A), 65.3 (Cquat, A), 104.8 (C tertiary OH, B), 171.0 (COO, A), 176.4 (COO, B), 214.7 (CO, A).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{18}O_4Na$: 237.1097; found: 237.1099.

Ethyl (*R*)-1-[(*R*)-4-Hydroxybutan-2-yl]-2-oxocyclopentane-1-carboxylate (3b)

Prepared according to the general bi-catalytic procedure (GP1) starting from β-keto ester **1b** (46.7 mg, 0.3 mmol) and allylic alcohol **2a** (32.4 mg, 0.45 mmol). The product was isolated as a pale yellow oil with >95:5 *dr*; yield: 38.9 mg (57%, 0.171 mmol); 86% *ee*.

The product was obtained as a mixture of open A and closed B forms in a 2.3:1 ratio; R_f = 0.17 (PE/EtOAc, 7:3); $[\alpha]_D^{20}$ –7.1 ($CHCl_3$, *c* = 0.45, 90% *ee* sample).

HPLC determination of the enantiomeric excess on the corresponding benzoyl protected alcohol prepared according to procedure C as reported in our earlier work.[5] Chiralpak AZ-H, hexane/*i*-PrOH (90:10), 1 mL/min, UV 220 nm: t_R (minor) = 15.7 min, t_R (major) = 17.1 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.8 Hz, CH_3, A), 1.1 (d, *J* = 6.8 Hz, CH_3, B), 1.22–2.30 (CH_3, A + B + 1 H of CH_2, A), 1.41–1.49 (m, 1 H of CH_2, B), 1.59–2.14 (m, 7 H, A + B + OH, A), 2.38–2.52 (m, 2 H, A + B), 3.58–3.65 (m, 1 H of CH_2, A + B + 1 H of CH_2, A), 4.08–4.20 (m, CH_2, A + B + 1 H of CH_2, B), 4.43 (br s, OH, B).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3, A), 14.1 (CH_3, B), 15.0 (CH_3, A), 16.8 (CH_3, B), 18.1 (CH_2, B), 19.7 (CH_2, A), 27.8 (CH_2, B), 28.1 (CH_2, A), 31.7 (CH, B), 31.9 (CH_2, B), 33.3 (CH, A), 36.0 (CH_2, A), 36.2 (CH_2, B), 39.0 (CH_2, A), 56.5 (Cquat, B), 56.5 (CH_2, B), 60.7 (CH_2, A), 61.0 (CH_2, B), 65.2 (Cquat, A), 104.8 (C tertiary OH, B), 171.5 (COO, A), 176.1 (COO, B), 214.8 (CO, A).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{20}O_4Na$: 251.1254: found: 251.1256.

***tert*-Butyl (*R*)-1-[(*R*)-4-Hydroxybutan-2-yl]-2-oxocyclopentane-1-carboxylate (3c)**

Prepared according to the general bi-catalytic procedure (GP1) starting from β-keto ester **1c** (55.1 mg, 0.3 mmol) and allylic alcohol **2a** (32.4 mg, 0.45 mmol). The product was isolated as a pale yellow oil with 95:5 *dr*; yield: 41.9 mg (54%, 0.163 mmol); 79% *ee*.

The product was obtained as a mixture of open A and closed B forms in a 2.3:1 ratio; R_f = 0.21 (PE/EtOAc, 7:3); $[\alpha]_D^{20}$ –5.9 ($CHCl_3$, *c* = 0.57, 79% *ee* sample).

HPLC determination of the enantiomeric excess on the corresponding benzoyl protected alcohol prepared according to procedure C as reported in our earlier work.[5] Lux-Cellulose-2, hexane/*i*-PrOH (95:5), 1 mL/min, UV 220 nm: t_R (major) = 9.3 min, t_R (minor) = 10.4 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.8 Hz, CH_3, A), 1.07 (d, *J* = 6.8 Hz, CH_3, B), 1.04–1.29 (m, 1 H, CH_2, A + B), 1.42 (s, *t*-C_4H_9, A), 1.47 (s, *t*-C_4H_9, B), 1.72–2.05 (m, 7 H, A + B), 2.36–2.45 (m, 2 H, H, A + B), 3.57–3.67 (m, CH_2 of A + 1 H of CH_2 B), 4.08 (ddd, *J* = 4.4, 3.8, 3.6 Hz, 1 H of CH_2, B), 4.66 (br s, OH, B).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (CH_3, A), 16.7 (CH_3, B), 18.1 (CH_2, B), 19.6 (CH_2, A), 27.8 (CH_3, A), 27.9 (CH_3, B), 28.0 (CH_2, A), 28.5 (CH_2, B), 31.4 (CH, B), 32.4 (CH_2, A), 32.9 (CH, A), 36.1 CH_2, A), 36.6 (CH_2, B), 38.8 (CH_2, A + B), 56.7 (Cquat, B), 58.7 (CH_2, B), 60.8 (CH_2, A), 69.0 (Cquat, A), 81.6 (C*t*-C_4H_9, B), 82.0 (C*t*-C_4H_9, A), 104.8 (C tertiary OH, B), 169.9 (COO, A), 175.8 (COO, B), 215.0 (CO, A).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{24}O_4Na$: 279.1567; found: 279.1570.

Methyl (*R*)-1-[(*R*)-1-Hydroxyhexan-3-yl]-2-oxocyclopentane-1-carboxylate

(Precursor to **5**, see SI for structure)

Prepared according to the general triple catalysis procedure (GP2) starting from β-keto ester **1a** (28.4 mg, 0.2 mmol) and allylic alcohol **2b** (R^3 = *n*-Pr; 40 mg, 0.4 mmol). Purification over silica gel (PE/EtOAc 9:1 to 8:2). The product was isolated as a pale yellow oil; yield: 13 mg (26%, 0.048 mmol). The *ee* was determined in the next step; R_f = 0.42 (PE/EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12–4.01 (m, 1 H of CH_2, B), 3.96 (br s, OH, B), 3.80–3.48 (m, 4 H, A and B + 1 H of CH_2, B), 2.58–2.33 (m, 1 H, A and B), 2.27–1.89 (m, 3 H, A and B), 1.87–1.50 (m, 5 H, A and B), 1.50–1.36 (m, 1 H, A and B), 1.33–1.05 (m, 1 H, A and B), 0.95–0.72 (m, CH_3, A and B).

13C NMR (75 MHz, $CDCl_3$): δ = 214.8 (CO, A), 175.9 (COOR, A), 171.2 (COOR, B), 104.9 (Cquat, B), 65.8 (Cquat, B), 61.4 (CH_2, B), 60.2 (CH_2, A), 57.3 (Cquat, A), 52.7 (CH_3, B), 51.3 (CH_3, A), 39.1 (CH_2, A), 38.5 (CH, B), 37.6 (CH, A), 35.4 (CH_2, B), 35.6 (CH_2, A), 34.8 (CH_2, B), 32.8 (CH_2, A), 31.9 (CH_2, B), 28.8 (CH_2, B), 24.5 (CH_2, A), 21.7 (CH_2, B), 21.0 (CH_2, A), 19.6 (CH_2, B), 18.3 (CH_2, A), 14.2 (CH_3, B), 13.9 (CH_3, A).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{22}O_4Na$: 265.1509; found: 265.1508.

Methyl (*R*)-1-[(*R*)-1-Hydroxy-5-phenylpentan-3-yl)-2-oxocyclopentane-1-carboxylate

(Precursor to **6**, see SI for structure)

Prepared according to the general triple catalytic procedure (GP2) starting from β-keto ester **1a** (28.4 mg, 0.2 mmol) and allyllic alcohol **2c** (R = CH_2CH_2Ph; 65 mg, 0.4 mmol) and purified by chromatography over alumina (PE/EtOAc 9:1). The product was isolated as a yellow oil; yield: 35 mg (57%, 0.115 mmol). The *ee* was determined in the next step; R_f = 0.47 (PE/EtOAc 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–6.99 (m, 5 H_{arom}), 4.10–3.95 (m, 1 H of CH_2, B), 3.70–3.50 (m, 4 H, A and B), 2.77–2.29 (m, 3 H, A and B), 2.18–1.33 (m, 10 H, A and B).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.6 (CO, A), 175.7 (COOR, A), 171.0 (COOR, B), 141.9 (Cquat, B), 141.7 (Cquat, A), 128.7 (2 × CH, A), 128.7 (2 × CH, B), 128.5 (2 × CH, B), 128.3 (2 × CH, A), 126.2 (CH, A), 125.7 (CH, B), 111.3 (Cquat, B), 75.3 (Cquat, A), 65.2 (Cquat, B), 60.6 (CH_2, A), 60.5 (CH_2, B), 55.6 (CH_3, A), 52.7 (CH_3, B), 38.2 (CH_2, B), 37.6 (CH_2, A), 35.5 (CH_2, B), 35.4 (CH_2, A), 33.9 (CH_2, B), 33.7 (CH_2, A), 33.1 (CH_2, A), 28.6 (CH_2, B), 28.0 (CH_2, A), 24.5 (CH, B), 21.2 (CH_2, B), 20.3 (CH_2, A), 18.6 (CH_2, A), 17.4 (CH_2, B).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}O_4Na$: 326.9825; found: 326.9825.

Methyl (*R*)-1-[(*R*)-4-Hydroxybutan-2-yl)-4,4-dimethyl-2-oxocyclopentane-1-carboxylate

(Precursor to **7**, see SI for structure)

Prepared according to the general triple catalytic procedure (GP2) starting from β-keto ester **1d** (28.5 mg, 0.17 mmol) and allylic alcohol **2a** (25 mg, 0.34 mmol). The product was purified by chromatography over silica gel (PE/EtOAc 8:2) and isolated as a pale yellow oil; yield: 9 mg (23%, 0.038 mmol). The *ee* was determined in the next step; R_f = 0.23 (PE/EtOAc 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.70 (br s, OH, B), 4.21–4.04 (m, 1 H of CH_2, B), 3.81–3.54 (m, 4 H, A and B + 1 H of CH_2, B), 2.54–2.23 (m, 1 ,H A and B), 2.10–1.72 (m, 4 H, A and B), 1.71–1.42 (m, 1 H, A and B), 1.43–1.16 (m, 3 H, A and B), 1.13–0.77 (m, 9 H, A and B).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.2 (CO, A), 178.0 (COOR, B), 171.7 (COOR, A), 104.6 (Cquat, B), 66.0 (Cquat, A), 60.7 (CH_2, A), 57.8 (CH_2, B), 57.2 (Cquat, B), 54.3 (CH_2, A), 52.7 (CH_3, A), 51.9 (CH_2, B), 51.8 (CH_3, B), 47.2 (CH_2, B), 41.9 (CH_2, A), 35.6 (CH, A), 35.5 (CH_2, B), 32.9 (Cquat, A), 32.4 (CH_3, B), 32.3 (Cquat, B), 31.9 (CH_3, B), 31.5 (CH, B), 30.5 (CH_3, A), 29.1 (CH_3, A), 27.5 (CH_2, A), 16.7 (CH_3, B), 15.2 (CH_3, A).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{22}O_4Na$: 265.1516; found: 265.1518.

Methyl (4*R*)-2-Hydroxy-2,4-dimethyltetrahydro-2*H*-pyran-3-carboxylate (10)

Prepared according to the triple-catalysis general procedure (GP2) using **Cat2**, β-keto ester **9** (24.6 mg, 0.21 mmol), and allylic alcohol **2a** (30 mg, 0.42 mmol), and purified by chromatography over silica gel (PE/EtOAc 9:1). The product was isolated as a yellow oil; yield: 24 mg (60%, 0.128 mmol); 90% *ee*; >99:1 *dr*; R_f = 0.42 (PE/EtOAc 7:3).

GC enantiomeric excess determination: Lipodex, method: 0 min at 90 °C, then 1 °C/min to 225 °C, t_R (minor) = 16.82, t_R (major) = 19.47 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.12–4.00 (m, 1 H of CH_2), 3.83–3.60 (m, 4 H, CH_3 + 1 H of CH_2), 2.30–2.07 (m, 2 H), 1.66–1.53 (1 H + OH), 1.47–1.20 (m, 4 H, CH_3 + 1 H), 0.90 (d, *J* = 5.9 Hz, CH_3, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5 (COOR), 94.1 (Cquat), 60.4 (CH_2), 57.6 (CH_3), 51.9 (CH), 32.7 (CH_2), 29.2 (CH), 28.8 (CH_3), 20.2 (CH_3).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_9H_{17}O_4$: 189.1117; found: 189.1117.

Spirolactone Formation; General Procedure

To a solution of the corresponding cascade adduct in anhyd toluene (0.17 M) was added DBU (1.9 equiv). The mixture was then stirred at r.t. (22–25 °C) for 2 h. Then, aq 1 M HCl (1.5 mL) was added. The aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed under vacuum. Purification over silica gel (PE/EtOAc, unless otherwise specified) afforded the expected lactone.

One-Pot Spirolactonization; (5*R*,10*R*)-10-Methyl-7-oxaspiro[4.5]decane-1,6-dione (4); Typical Procedure

To a solution of keto ester **1a** (28.4 mg, 0.2 mmol, 1 equiv) in anhyd xylene (0.6 mL) was added successively, allylic alcohol **2a** (34 µL, 0.4 mmol, 2 equiv), $Cu(acac)_2$ (2.4 mg, 0.01 mmol, 5 mol%), **Cat1** (9.4 mg, 0.026 mmol, 13 mol%). **[Fe]** complex (5.4 mg, 0.013 mmol, 6.5 mol%) and $Me_3NO{\cdot}2H_2O$ (1.8 mg, 0.016 mmol, 8 mol%) were added all at once. Argon was immediately passed through the vial for 20 seconds, the vial was closed and the contents were stirred at 10 °C. After completion of the reaction, DBU (1.9 equiv) was added and the reaction mixture was stirred for 1 h at 40 °C. Sat. aq NH_4Cl (1.5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed under vacuum. Purification over silica gel (PE/EtOAc, unless otherwise specified) afforded the expected lactone **4** (see below for analytical and spectral data).

(5*R*,10*R*)-10-Methyl-7-oxaspiro[4.5]decane-1,6-dione (4)

Prepared according to the general procedure starting from **3a** (23 mg, 1.07 mmol) and purified by chromatography over silica gel (PE/EtOAc 8:2). The product was isolated as a pale yellow oil; yield: 18 mg (92%, 0.099 mmol); 90% *ee*; R_f = 0.37 (PE/EtOAc 7:3); $[\alpha]_D^{20}$ –13.5 ($CHCl_3$, *c* = 1.1; 99:1 *dr*, 92% ee).

GC enantiomeric excess determination: Hydrodex, method: 0 min at 90 °C then 1 °C/min to 220 °C, t_R = 57.023 min, t_R = 57.825 min, t_R = 61.5 min, t_R = 62.4 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50–4.27 (m, 2 H), 2.70–2.54 (m, 1 H of CH_2), 2.52–2.43 (m, 1 H of CH_2), 2.34–2.09 (m, 4 H), 2.04–1.86 (m, 2 H), 1.75–1.64 (m, 1 H), 0.94 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.3 (CO), 171.8 (COOR), 67.5 (CH_2), 61.2 (Cquat), 37.6 (CH_2), 29.6 (CH), 26.7 (CH_2), 20.1 (CH_2), 16.5 (CH_2), 14.8 (CH_3).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{15}O$: 3183.1012; found: 183.1012.

(5*R*,10*R*)-10-Propyl-7-oxaspiro[4.5]decane-1,6-dione (5)

Prepared according to the general procedure starting from the corresponding cascade adduct (12 mg, 0.048 mmol) and purified by chromatography over silica gel (PE/EtOAc 9:1 to 8:2). The product was isolated as a pale yellow oil; yield: 10 mg (96%, 0.046 mmol); 90% *ee*; R_f = 0.42 (PE/EtOAc 7:3); $[\alpha]_D^{20}$ –67.5 ($CHCl_3$, *c* = 0.9; 99:1 *dr*, 93% ee).

GC enantiomeric excess determination: Hydrodex, method: 0 min at 90 °C then, 1 °C/min to 225 °C, t_R (major) = 75.23 min, t_R (minor) = 74.83 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.45–4.38 (m, 2 H), 2.63–2.55 (m, 2 H), 2.39–2.07 (m, 4 H), 1.93–1.77 (m, 2 H), 1.70–1.63 (m, 1 H), 1.31–1.19 (m, 4 H), 0.89 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.6 (CO), 171.5 (COOR), 69.3 (CH_2), 60.2 (Cquat), 39.06 (CH_2), 36.6 (CH), 32.7 (CH_2), 30.5 (CH_2), 24.9 (CH_2), 20.5 (CH_2), 19.4 (CH_2), 14.0 (CH_3).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd $C_{12}H_{19}O_3$: 211.1327; found: 211.1324.

(5*R*,10*R*)-10-Phenethyl-7-oxaspiro[4.5]decane-1,6-dione (6)

Prepared according to the general procedure starting from the corresponding cascade adduct (35 mg, 0.115 mmol) and purified by chromatography over silica gel (PE/EtOAc 9:1). The product was isolated as a pale yellow oil; yield: 27 mg (86%, 0.099 mmol); 93% *ee*; R_f = 0.47 (PE/EtOAc, 7:3); $[\alpha]_D^{20}$ –14 ($CHCl_3$, *c* = 0.7; 99:1 *dr*, 93% ee).

HPLC enantiomeric excess determination: Lux-Cellulose-4, heptane/EtOH (80:20), 1 mL/min, t_R (minor) = 11.46 min, t_R (major) = 12.55 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 2 H), 7.24–7.17 (m, 1 H), 7.16–7.12 (m, 2 H), 4.50–4.44 (m, 1 H of CH_2), 4.40–4.32 (m, 1 H of CH_2), 2.78–2.49 (m, 3 H), 2.44–2.35 (m, 1 H), 2.33–2.07 (m, 5 H), 1.95–1.87 (m, 1 H), 1.78–1.66 (m, 1 H), 1.60–1.37 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.4 (CO), 171.3 (COOR), 141.0 (Cquat$_{arom}$), 128.6 (CH_{arom}), 128.2 (CH_{arom}), 126.3 (CH_{arom}), 69.2 (CH_2), 60.3 (Cquat), 38.9 (CH_2), 36.7 (CH), 33.8 (CH_2), 32.6 (CH_2), 30.5 (CH_2), 24.9 (CH_2), 19.4 (CH_2).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}O_3$: 273.1478; found: 273.1480.

(5*R*,10*R*)-3,3,10-Trimethyl-7-oxaspiro[4.5]decane-1,6-dione (7)

Prepared according to the general procedure starting from the corresponding cascade adduct (10 mg, 0.037 mmol) and purified by chromatography over silica gel (PE/EtOAc 8:2). The product was isolated as a pale yellow oil; yield: 8 mg (90%, 0.034 mmol); 90% *ee*; R_f = 0.51 (PE/EtOAc 7:3); $[\alpha]_D^{20}$ −12.6 ($CHCl_3$, *c* = 0.6; 99:1 *dr*, 93% ee).

GC enantiomeric excess determination: Lipodex, method: 60 min at 120 °C then 1 °C/min to 225 °C, t_R (major) = 71.08 min, t_R (minor) = 83.43 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41 (dd, *J* = 7.0, 5.6 Hz, 2 H), 2.61 (d, *J* = 17.6 Hz, 1 H of CH_2, AB), 2.46–2.37 (m, 1 H), 2.27 (d, *J* = 14.2 Hz, 1 H of CH_2, AB), 2.21 (d, *J* = 17.6 Hz, 1 H of CH_2, AB), 2.15–2.07 (m, 1 H of CH_2), 2.01 (d, *J* = 14.1 Hz, 1 H of CH_2, AB), 1.65–1.55 (m, 1 H of CH_2), 1.25 (s, CH_3, 3 H), 1.14 (s, CH_3, 3 H), 0.98 (d, *J* = 6.8 Hz, CH_3, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.1 (CO), 171.9 (COOR), 68.2 (CH_2), 61.9 (Cquat), 53.9 (CH_2), 43.9 (CH_2), 32.9 (Cquat), 32.4 (CH), 30.8 (CH_3), 30.1 (CH_3), 27.1 (CH_2), 16.4 (CH_3).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{19}O_3$: 211.1327; found: 211.1325.

(3*R*,4*R*)-3-Acetyl-4-methyltetrahydro-2*H*-pyran-2-one (11)

To a solution of **10** (100 mg, 0.53 mmol) in anhyd toluene (3 mL, 0.17 M) was added DBU (152.0 mg, 1.0 mmol, 1.9 equiv). The mixture was heated in a microwave oven for 60 min at 60 °C. Then, aq 1 M HCl (1.5 mL) was added. The aqueous layer was extracted with Et_2O (3 × 2 mL). of The combined organic phases were dried (Na_2SO_4) and the solvent was removed under vacuum. Purification by chromatography over silica gel (PE/CH_2Cl_2 5:5) afforded **11** as a colorless oil; yield: 43 mg (52%, 0.2756 mmol); >20:1 *dr*. The product was obtained in a 1:1 ratio between ketone A and enol B forms; R_f = 0.43 (PE/EtOAc 8:2); $[\alpha]_D^{20}$ −67.6 ($CHCl_3$, *c* = 1.0; 99:1 *dr*, 90% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.9 (s, 1 H, A), 4.49–4.24 (m, 4 H, A and B), 3.27 (d, *J* = 9.3 Hz, 1 H, A), 2.86–2.78 (m, 1 H, B′), 2.57–2.46 (m, 1 H, A), 2.37 (s, 3 H, A), 2.14–1.92 (m, 5 H, A′ and B), 1.72–1.50 (m, 2 H, B), 1.15 (d, *J* = 7.1 Hz, 3 H, B), 1.05 (d, *J* = 6.6 Hz, 3 H, A).

13C NMR (75 MHz, $CDCl_3$): δ = 202.7 (A), 176.1 (B), 172.6 (B), 167.8 (A), 98.9 (B), 68.4 (A), 64.6 (B), 61.8 (A), 30.6 (A), 29.7 (A), 29.1 (B), 28.6 (A), 26.2 (B), 20.4 (A), 20.2 (B), 18.1 (B).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{13}O_3$: 157.0856; found: 157.0857.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588547.

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