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Copper-Catalyzed Asymmetric Allylic Alkylation of Halocrotonates: Efficient Synthesis of Versatile Chiral Multifunctional Building Blocks

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Abstract: The highly enantioselective synthesis of α -methyl-substituted esters is reported in up to 90% yield and up to 99% *ee* using copper-TaniaPhos as chiral catalyst. The transformation proved scalable to at least 6.6 mmol (1.7 g scale). The products of this transformation have been further elaborated to multifunctional building blocks with a single (branched

esters and acids) or multiple stereogenic centers (vicinal dimethyl esters, as well as, hydroxy- or iodo-substituted lactones).

Keywords: asymmetric catalysis; carbon-carbon bond formation; copper catalysis; Grignard reagents; multifunctional building blocks

Introduction

Small, enantiopure multifunctional building blocks are frequently selected as the synthons of choice in retrosynthetic analyses of complex natural products.^[1] Cu-catalyzed asymmetric allylic alkylation (AAA)^[2] is one of the emerging methodologies for the asymmetric formation of C–C bonds and has been used to prepare a variety of multifunctional building blocks.^[3]

In our ongoing program to broaden the scope of the Cu-catalyzed AAA^[3b,4] and asymmetric conjugate addition (ACA)^[5] with Grignard reagents, we recently have focussed our attention towards novel substrates

with multiple reactive sites. Recent examples of chemo-, regio- and enantioselective reactions of this type are the hetero-AAA^[4c] [Scheme 1, Eq. (a)] and the asymmetric 1,6-addition^[6] [Scheme 1, Eq. (b)]. In the hetero-AAA, using Cu catalysis employing TaniaPhos (**L1**, Figure 1), S_N2' addition is favored over 1,4-addition, 1,2-addition and S_N2 addition.^[4c] In the asymmetric 1,6-addition, the use of Cu catalysis employing reversed Josiphos (**L2**), favors addition to the δ -position (1,6-addition) over addition to either the β -position (1,4-addition) or addition to the ester functionality (1,2-addition).^[6]

Scheme 1. Asymmetric Cu-catalyzed hetero-AAA (a) and 1,6-addition (b).

Figure 1. Chiral ferrocenyl-based phosphines used in AAA and ACA of Grignard reagents. Cy = cyclohexyl.

Figure 2. Desired allylic alkylation of 4-halocrotonates with Grignard reagents. X = halogen.

Other substrates with chemo-, regio-, and stereoselectivity issues are 4-halocrotonates (Figure 2). For these substrates organometallic reagents can attack on every C-atom. Our current challenge is to selectively achieve asymmetric Cu-catalyzed S_N2' -addition with reactive Grignard reagents.

The use of 4-halocrotonates in allylic alkylation was pioneered by Hoveyda and co-workers.^[7] Using a combination of $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ and chiral peptidic Schiff base ligands for the AAA of a variety of dialkylzinc reagents, tertiary^[7a] and quaternary carbon centers^[7b] were constructed with high regioselectivity and *ee*. This methodology requires the use of 6 equivalents of Me_2Zn for the construction of the prominent Me-substituted tertiary carbon centers^[8] with high *ee* (90%).^[7a] Recently, 4-halocrotonates were transformed in the Cu-free AAA^[7c] of selected Grignard reagents using N-heterocyclic carbene ligands with moderate *ee*.

Although α -alkyl-substituted acids, amides and esters are abundant in nature, the building blocks prepared *via* AAA have, so far, only seen limited use in natural product synthesis.^[7a,9] This lack of application might be due to the stereogenic center α to the ester moiety which is prone to epimerization.

In this paper we describe the highly selective AAA of MeMgBr (only 1.2 equiv. required) to 4-bromocrotonates using Cu catalysis with the commercially available TaniaPhos (**L1**). Furthermore, we describe the

elaboration of the allylic alkylation products to a variety of versatile acyclic and cyclic multifunctional building blocks with a single or with multiple stereogenic centers. The described transformations illustrate that, with optimized methods, the sensitive α -Me substituted β,γ -unsaturated esters can be successfully elaborated and thus represent a highly versatile addition to the current building blocks and our repertoire for the preparation of natural products.

Results and Discussion

We initially chose the Br-substituted α,β -unsaturated ester **5a** (Table 1), synthesized in 2 steps from crotonic acid (see Experimental Section for preparation), as substrate^[10] and focused on a regioselective addition of MeMgBr ^[11] (Table 1). Using non-ligated $\text{CuBr} \cdot \text{SMe}_2$ at -40°C or employing either reversed JosiPhos (**L2**) or JosiPhos (**L3**) at -78°C in CH_2Cl_2 , a mixture of S_N2 (**7a**) and S_N2' products (**6a**) was obtained (entries 1–3). However, the use of TaniaPhos (**L1**) gave selectively the S_N2' product (**6a**, entry 4). When the more reactive Michael acceptor **5b** was used in combination with **L1**, a mixture of α -substituted alkyl thioester **6b** and cyclopropane **8b** was found. The formation of the latter product is attributed to a

Table 1. Ligand screening for regioselective S_N2' -alkylation using MeMgBr .^[a]

Entry	R	Ligand	Conversion ^[b]	6 ^[b]	7 ^[b]	8 ^[b]
1	OBn	none ^[c]	full	50%	50%	–
2	OBn	L2 ^[d]	93%	52%	27%	–
3	OBn	L3 ^[d]	76% ^[e]	31%	26%	–
4	OBn	L1	full	> 95%	< 5%	–
5	SEt	L1 ^[f]	full	49%	–	47%

^[a] Conditions: **5a** or **5b** (1 equiv.) in CH_2Cl_2 was added to a solution of MeMgBr (3.0 M in Et_2O , 1.2 equiv.), ligand (1.1 mol%) and $\text{CuBr} \cdot \text{SMe}_2$ (1 mol%) in CH_2Cl_2 (0.2 M in **5**).

^[b] Conversion and % **6**, **7** and **8** are determined by GC-MS and correlate approximately with the ratio observed by ^1H NMR.

^[c] $\text{CuBr} \cdot \text{SMe}_2$ (1 equiv.) was used at -40°C .

^[d] **L3** (2.2 mol%) and $\text{CuBr} \cdot \text{SMe}_2$ (2 mol%) were used.

^[e] 19% of benzylcrotonate obtained (see further ref.^[14]).

^[f] **L1** (5.5 mol%) and $\text{CuBr} \cdot \text{SMe}_2$ (5 mol%) were used.

Table 2. AAA of MeMgBr to **5a** at increasing quantity.^[a]

Entry	Scale	Reaction Time	Yield	ee ^[b]
1	0.5 mmol, 0.12 g	2 h	86%	99%
2 ^[c]	2.0 mmol, 0.51 g	40 h	81% ^[d]	96% ^[d]
3	2.5 mmol, 0.64 g	16 h	88%	98%
4	4.0 mmol, 1.02 g	16 h	87%	98%
5	6.6 mmol, 1.68 g	16 h	90%	98%

^[a] Conditions: **5a** (1 equiv.) in CH₂Cl₂ was added to a solution of MeMgBr (3.0 M in Et₂O, 1.2 equiv.), **L1** (1.1 mol%) and CuBr·SMe₂ (1 mol%) in CH₂Cl₂ (0.2 M in **5a**).

^[b] Determined by chiral HPLC.

^[c] (*S,S*)-**L1** was used and (*R*)-**6a** was obtained.

^[d] See ref.^[16]

tandem 1,4-addition–intramolecular enolate trapping.^[12,13]

The addition of MeMgBr to **5a** using only 1 mol% Cu-TaniaPhos catalyst at a 0.5 mmol scale provides

product **6a** (Table 2, entry 1) in excellent yield (86%) and *ee* (99%). This is the highest *ee* so far for the introduction of a methyl group *via* AAA. Furthermore, only traces (<5%) of the S_N2 product were observed. Performing the reaction in up to 6.6 mmol (1.7 g) scale^[15] gave the product again in excellent yields and enantioselectivities, albeit with somewhat longer reaction times (entries 2–5). Using (*S,S*)-TaniaPhos for the transformation led to the opposite enantiomer of the product with high *ee* (entry 2).^[16]

Elaboration of the products to multifunctional building blocks proved challenging due to the ready isomerization of the β,γ-unsaturated ester to the conjugated α,β-unsaturated ester. However, we were able to obtain several chiral building blocks derived from (*S*)-**6a** in high *ee* and yield.

First of all, we focused on orthogonally reducing either the olefin or liberating the carboxylic acid [Scheme 2, Eqs. (a), (b)]. The reduced protected chiral α-Me substituted esters like (*S*)-**10** are highly desired building blocks and have been used previously for the synthesis of a pheromone of the male mouse, *Mus musculus*,^[17] and the synthesis of several fragrances.^[18] We were able to reduce the olefin in high yield retaining the chiral integrity of the α-Me center, without deprotection of the ester [Scheme 2, Eq (a)].^[19,20]

Scheme 2. Synthesis of multifunctional building blocks incorporating a single stereogenic center starting from olefin **6a**. Conditions: (a) **6a** (1 equiv.), **9** (20 mol%), hydrazine hydrate (10 equiv.), EtOH (0.11 M in **6a**), room temperature, 2 h. (b) **6a** (1 equiv.), BBr₃ (1.5 equiv.), CH₂Cl₂ (0.22 M in **6a**), –78 °C, 10 min, 0 °C, 2 h. (c) 1) **6a** (1 equiv.), 9-BBN (0.5 M solution in THF, 2.5 equiv.), THF (total 0.29 M in **6a**), 0 °C to room temperature, 1.5 h; 2) EtOH (3.5 equiv.), 0 °C; 3) H₂O₂ (~4.7 equiv.), phosphate buffer pH 7.0 (total THF and H₂O 0.13 M in **6a**).

Table 3. Reduction of the β,γ -unsaturated olefin of **6a**.^[a]

Entry	Reduction Method	Hydrazine	Time	Reduction ^[b]	Isomerization ^[b]
1	Pd/C (0.25%)	—	1 h	full	24%
2	9 (5%)	20 equiv.	4 h	full ^[c]	< 5%
3	9 (20%)	10 equiv. ^[d]	2 h	full	< 5%

^[a] Conditions: **6a** (1 equiv.), Pd/C (5 wt%), EtOAc (0.2 M in **6a**), room temperature or **6a** (1 equiv.), **9**, hydrazine hydrate, EtOH (0.11 M in **6a**), room temperature.

^[b] Reduction and isomerization were determined by GC-MS and correlate with the ratio observed by ¹H NMR.

^[c] 10% BnOH observed.

^[d] Slow addition of **9** and hydrazine hydrate.

In initial attempts employing hydrogenation catalyzed by Pd on coal we observed substantial isomerization (Table 3, entry 1). Using our recently developed method for olefin reduction by diimide, generated *in situ* from hydrazine and a cheap vitamin B₂ derivative **9**,^[21] we obtained full conversion with only traces of isomerization (entries 2 and 3). It must be noted that a slow addition protocol was required to prevent the reaction of hydrazine with the ester moiety.

Vice versa, deprotection of the carboxylic acid leaving the olefin intact, proceeded in good yield with only marginal loss of enantiopurity [Scheme 2, Eq. (b)].^[22] Initial attempts to deprotect (*S*)-**6a** using either base (Table 4, entries 1 and 2) or acid (entry 3) gave extensive isomerization. Lewis acidic mediated deprotection employing BBr₃, gave a clean reaction

with only trace amounts of the isomerized product (entry 4).^[23] Previously, the racemic building block **11** has been used for the synthesis of racemic multistriatin.^[24]

Another important building block could be obtained *via* a hydroboration-oxidation sequence leading to the terminal alcohol (*S*)-**12**.^[25] This compound has been used previously for the synthesis of sea food odours^[25a] and the synthesis of four stereoisomers of the phytophthora $\alpha 1$ mating hormone.^[25d] Using an excess of 9-BBN, subsequent oxidation at pH 7 with strict control of the reaction time, (*S*)-**12** was obtained in good yield [Scheme 2, Eq. (c)]. Presumably the first equivalent of 9-BBN coordinates to the ester as witnessed from the low conversion with 1.2 and 1.5 equivalents of 9-BBN (Table 5, entries 1 and 2). Furthermore, extended reaction times or a basic reaction medium in the oxidation step cause lactonization.^[26]

Table 4. Deprotection of the carboxylic acid of **6a**.^[a]

Entry	Method	Conversion ^[b]	Isomerization ^[b]
1	LiOH	> 95%	53%
2	LiOH, LiCl, H ₂ O ₂	78%	81%
3	TFA	35%	30%
4	BBr ₃	> 95%	< 5%

^[a] Conditions: **6a** (1 equiv.), LiOH (3 equiv.), H₂O/THF (4/1, 0.1 M in **6a**), room temperature, 16 h or **6a** (1 equiv.), LiOH (3 equiv.), LiCl (3 equiv.), H₂O₂ (6 equiv.), H₂O/THF (4/1, 0.1 M in **6a**), room temperature, 6 h or **6a** (1 equiv.), TFA (7 equiv.), H₂O (0.1 M in **6a**), room temperature, 64 h or **6a** (1 equiv.), BBr₃ (1.5 equiv.), CH₂Cl₂ (0.22 M in **6a**), −78 °C, 10 min, 0 °C, 2 h.

^[b] Conversion and isomerization were determined by ¹H NMR.

Table 5. Optimization of the stoichiometry of 9-BBN for the hydroboration of **6a**.^[a]

Entry	Equiv. of 9-BBN	Conversion ^[b]
1	1.2	traces
2	1.5	3%
3	2.0	> 95%

^[a] Conditions: **6a** (1 equiv.), 9-BBN (0.5 M solution in THF), THF (total 0.29 M in **6a**).

^[b] Conversion from (*S*)-**6a** to (*S*)-**13** was determined by GC-MS.

Table 6. Ligand and additive screening for the cross metathesis of **6a** with 1-octene.^[a]

Entry	Catalyst	Additive	Conversion ^[b]	Isomerization ^[b]
1	Grubbs I	—	62%	86%
2	Grubbs II	—	92%	27%
3	Hoveyda-Grubbs I	—	68%	3%
4	Hoveyda-Grubbs II	—	full	76%
5	Hoveyda-Grubbs II	Cl ₂ BQ	full	< 5%

^[a] Conditions: **6a** (1 equiv.), 1-octene (2 equiv.), catalyst (5 mol%), 2,6-dichlorobenzoquinone (10 mol%), CH₂Cl₂ (0.25 M in **6a**), 40 °C, 16 h.

^[b] Conversion and isomerization were determined by GC-MS and correlate with the ratio observed by ¹H NMR.

Cross metathesis (CM) starting from building block **6a** has been used previously to prepare (*R*)-elenic acid^[7a] by Hoveyda and co-workers. This particular CM with a challenging disubstituted terminal olefin yielded the intended product in low conversion.^[7a] We envisioned that CM could modularly produce a variety of α -Me esters.^[27] Initial attempts using CM catalysts gave either extensive isomerization (Table 6, entries 1, 2 and 4) or low conversion (entry 3). However, employing 2,6-dichlorobenzoquinone as additive,^[28] presumably preventing the formation of RuH,^[28a] the *E*-CM products were obtained in good conversion and only traces of isomerization product were observed (entry 5).

Using these optimized conditions, a variety of olefins could be coupled to **6a** (Table 7, entries 1, 3 and 4). Coupling, however, of an olefin bearing an unprotected hydroxy group gave extensive isomerization (entry 2).

A substrate class closely related to the cross-metathesis products are the α -Me-substituted saturated esters.^[29] These building blocks have been previously used for the synthesis of an alarm pheromone of *Atta texana*,^[30] a high-potency sweetener NC-00637,^[29a] and

candidates for a tuberculosis vaccine.^[31] We envisioned that these building blocks could be modularly constructed by a CM–olefin reduction sequence from **6a**. With optimized conditions^[21] for the non-transition metal-mediated reaction we were able to obtain (*S*)-**15** in 89% conversion and 75% yield (Scheme 3) illustrating the possibility of assembling these highly warranted products using AAA.

After completing the synthesis of a number of building blocks with a single stereogenic center, we turned our attention to preparation of building blocks with multiple stereogenic centers. To obtain *anti*-vicinal dimethyl motifs,^[4d,32] the CM product (*S,E*)-**14d** was converted to (*S*)-**16** in good yield and reasonable regioselectivity (Scheme 4).^[33]

A very interesting motif in the context of natural product synthesis is the propionate unit. Using typical Sharpless asymmetric dihydroxylation conditions, several ligands were screened for the preparation of this structural entity (Table 8).^[34] Using methylsulfonamide^[35] to speed up the dihydroxylation of **6a**, ligand **L5** proved superior for the preparation of the *anti*- β -hydroxy- γ -butyrolactone (entry 2) and **L6** gave the best results for the *syn*- β -hydroxy- γ -butyrolactone

Table 7. Cross metathesis of **6a** with a variety of olefins.^[a]

olefin, HG-II
2,6-dichlorobenzoquinone
CH₂Cl₂
40 °C

(S)-**6a** → (S,E)-**14**

Entry	Olefin	Product	Time	Yield	Isomerization ^[b]
1		14a	8 h	84%	< 5%
2 ^[c]		14b	16 h	nd (91%) ^[d]	91%
3		14c	8 h	66%	< 5%
4		14d	16 h	73% ^[e]	< 5%

^[a] Conditions: **6a** (1 equiv.), olefin (2 equiv.), HG-II (5 mol%), 2,6-dichlorobenzoquinone (10 mol%), CH₂Cl₂ (0.25 M in **6a**), 40 °C, 16 h.

^[b] % isomerization is determined by ¹H NMR.

^[c] 10 mol% HG-II and 20 mol% 2,6-dichlorobenzoquinone were used.

^[d] Conversion, determined by GC-MS.

^[e] Product was obtained in 96% *ee*.

Scheme 3. Synthesis of α -Me-substituted esters. Conditions: see Table 7 for CM. **14a** (1 equiv.), **9** (1 equiv.), hydrazine hydrate (50 equiv.), EtOH (0.11 M in **14a**), room temperature, O₂ atmosphere, 5 h, addition under vigorous stirring, additional 1 h vigorous stirring.

Scheme 4. Synthesis of a vicinal dimethyl motif. Conditions: see Table 7 for CM. **14d** (1 equiv.), MeMgBr (2 equiv.), CuCN (2 equiv.), Et₂O/CH₂Cl₂ (2:3, 0.1 M in **14d**), −40 °C, 16 h.

(entry 3).^[36] In all cases the lactonized products were obtained as a single diastereomer in reasonable yields and high *ee* (Scheme 5). The propionate building blocks have been used previously for the syntheses of (−)- α -multistriatin^[33c] and apoptolidinone.^[37]

Finally, when the deprotected β,γ -unsaturated carboxylic acid (*S*)-**11** was subjected to iodolactonization using Barluenga's reagent^[38,39] the 5-membered lactone [Scheme 6, Eq. (b)] was obtained albeit in a low yield.^[40] Performing the iodolactonization employing I₂ and K₃PO₄ in CH₂Cl₂ the 4-membered lactone [Scheme 6, Eq. (a)] could be obtained.^[41,42]

2,4-Disubstituted 3-butyrolactones^[43] (Scheme 7) are interesting building blocks for natural product synthesis and have been used, for example, in the synthesis of jasplakinolide.^[44] We envisioned constructing these highly versatile structures with three contiguous

Scheme 5. Synthesis of lactonized propionate motifs. Conditions: see Table 8.

Table 8. Screening of ligands for the asymmetric dihydroxylation of a racemic mixture of **6a**.^[a]

Entry	Ligand	<i>ee anti</i> ^[b]	<i>ee syn</i> ^[b]
1	L4	60%	60%
2	L5 ^[c]	85%	64%
3	L6 ^[c]	70%	70%

^[a] Conditions: **6a** (1 equiv), **L** (2.5 mol%), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (1 mol%), K_2CO_3 (3 equiv.), K_3FeCN_6 (3 equiv.), $\text{H}_2\text{O}/t\text{-BuOH}$ (1:1, 0.1 M in **7**), 0°C , 16 h.

^[b] Determined by chiral GC. *ee anti* = $100 \times \{[(3S,3R)\text{-}\mathbf{18} - (3S,3R)\text{-}\mathbf{18}]/[(3S,4S)\text{-}\mathbf{18} + (3S,3R)\text{-}\mathbf{18}]\}$. *ee syn* = $100 \times \{[(3R,3R)\text{-}\mathbf{18} - (3R,4S)\text{-}\mathbf{18}]/[(3R,3R)\text{-}\mathbf{18} + (3R,4S)\text{-}\mathbf{18}]\}$.

^[c] MeSO_2NH_2 (1 equiv.) was used.

stereogenic centers by an AAA-CM-carboxylic acid deprotection-iodolactonization sequence. We man-

Scheme 6. Iodolactonization of **11** leading to 5- and 4-membered lactones. Conditions: (a) **11** (1 equiv.), $\text{I}(\text{pyr})_2\text{BF}_4$ (1.1 equiv.), HBF_4 (1.5 equiv.), CH_2Cl_2 (0.03 M in **11**), -78°C to -10°C , 1.5 h. (b) **11** (1 equiv.), I_2 (5 equiv.), K_3PO_4 (5 equiv.), CH_2Cl_2 (9.5 mM in **11**), room temperature, 40 h.

Scheme 7. Synthesis of 5-membered 2,4-disubstituted 3-iodobutyrolactones. Conditions: see Table 7 for CM. See Scheme 2, Eq. (b) for deprotection. **21** (1 equiv.), $\text{I}(\text{pyr})_2\text{BF}_4$ (1.1 equiv.), HBF_4 (1.5 equiv.), CH_2Cl_2 (0.03 M in **21**), -78°C to -10°C , 1.5 h.

aged to obtain **22** in good yield as the single 3,4-*trans*-4,5-*trans* diastereomer^[39,45] (Scheme 7) illustrating the potential of these transformations to modularly construct 5-membered 2,4-disubstituted 3-iodobutyrolactones.

Conclusions

In summary, we have developed a highly enantioselective allylic alkylation to benzyl 4-bromocrotonates leading to chiral α -Me-substituted esters. These products have been successfully elaborated to a variety of chiral multifunctional building blocks without significant loss of stereochemical integrity at the stereogenic center. Furthermore, the explored synthetic transformations on the AAA-product **6a** show great potential for the elaboration of related AAA products.

Experimental Section

General Procedures

Thin-layer chromatography (TLC) was performed on commercial Kieselgel 60 F₂₅₄ silica gel plates and compounds were visualized with KMnO₄ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with MgSO₄. Concentration of solutions was conducted with a rotary evaporator. Progress of the reactions and conversion was determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Enantio- and regioselectivities were determined by chiral GC (HP6890, ChiralDEX-B-PM 30 m × 0.25 mm × 0.25 µm; HP6890, ChiralSIL-DEX-CB 25 m × 0.25 mm × 0.25 µm) using flame ionization detection or HPLC analysis (Chiralcel AS-H, 4.6 × 250 mm, 5 m, 40 °C, 0.5 mL min⁻¹, 205 nm; Chiralcel OB-H, 4.6 × 250 mm, 5 m, 40 °C, 0.5 mL min⁻¹, 205 nm; Chiralcel OJ-H, 4.6 × 250 mm, 5 m, 40 °C, 0.5 mL min⁻¹, 205 nm) (in comparison to authentic samples of racemates of the products). Optical rotations were measured in CH₂Cl₂ or CHCl₃ on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). ¹H NMR spectra were recorded at 400 MHz with CDCl₃ as solvent (Varian AMX400 spectrometer). ¹³C NMR spectra were obtained at 100.59 MHz in CDCl₃. The nature of the carbon was determined from APT ¹³C NMR experiments. Chemical shifts were determined relative to the residual solvent peaks (CHCl₃, δ = 7.24 for hydrogen atoms, δ = 77.23 for carbon atoms). The following abbreviations were used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High resolution mass spectra were determined on an FT-MS Orbitrap FischerScientific mass spectrometer by ESI measurements in the positive mode. Fragmentation patterns were determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA).

All reactions under a N₂ atmosphere were conducted using standard Schlenk techniques. CH₂Cl₂ was distilled from CaH₂ under a N₂ atmosphere prior to use. Et₂O was distilled from Na using benzophenone as indicator under a N₂ atmosphere prior to use. THF was distilled from Na using benzophenone as indicator under a N₂ atmosphere prior to use. CuBr·SMe₂ was purchased from Sigma-Aldrich. (*R,R*)-TaniaPhos and (*S,S*)-TaniaPhos were purchased from Sigma-Aldrich. MeMgBr was purchased from Sigma-Aldrich. Grignard reagents were titrated using *s*-BuOH and catalytic amounts of 1,10-phenanthroline before use.

Crotonic acid, *N*-bromosuccinimide, DCC, EtSH, dichlorobenzoquinone, HG-II catalyst, imidazole, CuCN, K₂OsO₂(OH)₄, (DHQ)₂AQN, (DHQ)₂Phal and (DHQ)₂Pyr were purchased from Sigma-Aldrich. Azobis(isobutyronitrile) was purchased from Janssen Chimica. BnOH, H₂O₂ and K₃Fe(CN)₆ were purchased from Merck. DMAP, hydrazine hydrate, TBDPSCl and methanesulfonamide were purchased from ACROS. K₂CO₃ was purchased from Boom.

Bromination of Crotonic Acid^[46]

In a round-bottom flask equipped with stirring bar, crotonic acid (20 g, 0.23 mol, 1.0 equiv.) and *N*-bromosuccinimide (46 g, 0.25 mol, 1.1 equiv.) were dissolved in benzene (200 mL). After the solution was heated to reflux azobis(iso-

butyronitrile) (1.14 g, 6.97 mmol, 3 mol%) was added and refluxing was continued for 2 h. Then the reaction solution was cooled to 0 °C and filtered over celite. The residue was washed with toluene (50 mL). The filtrate was concentrated and recrystallized from toluene and afforded 4-bromocrotonic acid as a white solid in several batches.

(*E*)-4-Bromobut-2-enoic acid (4-bromocrotonic acid): yield: 70%; white solid; mp 74.7–75.3 °C. ¹H NMR: δ = 11.63 (s, br, 1H), 7.10 (dt, *J* = 7.3 Hz, 15.3 Hz, 1H), 6.03 (d, *J* = 15.4 Hz, 1H), 4.01 (d, *J* = 7.3 Hz, 2H), spectrum contains traces of crotonic acid; ¹³C NMR: δ = 171.3 (C), 144.65 (CH), 123.99 (CH), 28.86 (CH₂); MS: *m/z* = 166 (M⁺[⁸¹Br], 56), 164 (M⁺[⁷⁹Br], 56), 85 (M–Br, 100); HR-MS: *m/z* = 163.9471, calcd. for C₄H₅⁷⁹BrO₂: 163.9473.

General Procedure for the Esterification of 4-Bromocrotonic Acid

In a round-bottom flask equipped with stirring bar under a N₂ atmosphere, 4-bromocrotonic acid (1.0 equiv.), BnOH (1.1 equiv.) and DMAP (0.1 equiv.) were dissolved in CH₂Cl₂ (5 mL mmol⁻¹ 4-bromocrotonic acid), the solution was cooled to 0 °C and DCC (1.05 equiv.) was added. After addition the reaction mixture was stirred for 16 h at room temperature (real reaction time < 4 h). The reaction mixture was then filtered over celite and the residue washed with CH₂Cl₂ (30 mL). The combined organic extracts were dried and concentrated to a colorless oil. The product was purified by flash column chromatography (Et₂O:pentane 1:50) and subsequent recrystallization from pentane; yield (10 mmol scale): 66%; white solid.

Benzyl (*E*)-4-bromobut-2-enoate (5a): data in accordance with data described in ref.^[47] MS: *m/z* = 256 (M⁺[⁸¹Br], 1), 254 (M⁺[⁷⁹Br], 1), 175 (M–Br, 29), 156 (44), 107 (BnO, 28), 91 (Bn, 100).

Thioesterification of 4-Bromocrotonic Acid^[48]

In a round-bottom flask equipped with stirring bar under a N₂ atmosphere, 4-bromocrotonic acid (3.47 g, 21.0 mmol), EtSH (1.55 mL, 21.0 mmol) and DMAP (0.26 g, 2.10 mmol) were dissolved in CH₂Cl₂ (120 mL), the solution was cooled to 0 °C and DCC (4.76 g, 23.1 mmol) was added. After addition the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then filtered over celite and the residue washed with CH₂Cl₂ (30 mL). The combined organic extracts were washed with, subsequently, an aqueous NaHCO₃ solution (saturated, 150 mL), H₂O (150 mL) and a saturated brine solution (100 mL), dried and concentrated to a colorless oil. Flash chromatography (Et₂O:pentane 1:99) afforded **5b** as a colorless oil; yield: 70%.

***S*-Ethyl (*E*)-4-bromobut-2-enethioate (5b):** data in accordance with data described in ref.^[48]

General Procedure for the Asymmetric Allylic Alkylation with MeMgBr

In a dried Schlenk tube equipped with septum and stirring bar under a N₂ atmosphere, CuBr·SMe₂ (1.0 mol%) and (*R,R*)-TaniaPhos (1.1 mol%) were dissolved in anhydrous CH₂Cl₂ (4.0 mL mmol⁻¹ substrate). After 5 min stirring at room temperature the mixture was cooled to –78 °C and MeMgBr (Aldrich, 3.0 M solution in Et₂O, 1.2 equiv.) was

added. After stirring for an additional 10 min, a solution of substrate (1.0 equiv.) in anhydrous CH_2Cl_2 (additional 1.0 mLmmol^{-1} substrate) was added with a syringe pump over 0.5 h. The reaction mixture was stirred for 16 h at -78°C and subsequently EtOH (0.4 mLmmol^{-1} substrate) and an aqueous NH_4Cl solution (1 M, 2.0 mLmmol^{-1} substrate) were added. The mixture was warmed to room temperature and an additional 10 mLmmol^{-1} substrate of the NH_4Cl solution and 10 mLmmol^{-1} substrate of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 ($2 \times 10 \text{ mLmmol}^{-1}$ substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O :pentane 1:99) afforded the product as a colorless oil.

Benzyl (S)-2-methylbut-3-enoate (6a): yield (10 mmol scale): 89% yield, 96% *ee*; yield (6.6 mmol scale): 90%, 98% *ee*; yield (4 mmol scale): 88%, 98% *ee*; yield (2.5 mmol scale): 88%, 98% *ee*; yield (0.5 mmol scale): 86%, 99% *ee*, colorless oil; (*R*)-enantiomer: yield (2.0 mmol scale): 81%, 96% *ee*. $[\alpha]_{\text{D}}^{20}$: +19.0 (*c* 1.0, CH_2Cl_2), (*S*)-enantiomer: using (*S,S*)-TaniaPhos $[\alpha]_{\text{D}}^{20}$: -20.2 (*c* 1.0, CH_2Cl_2); (*R*)-enantiomer: lit.^[27] value for 10% *ee* $[\alpha]_{\text{D}}^{20}$: -1.5 (*c* 0.7, CH_2Cl_2); (*R*)-enantiomer. ^1H NMR: δ = 7.38–7.25 (m, 5H), 5.92 (ddd, *J* = 17.5 Hz, 10.2 Hz, 7.5 Hz, 1H), 5.17–5.04 (m, 4H), 3.23–3.13 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR: δ = 174.41 (C), 137.17 (CH), 136.19 (C), 128.70 (CH), 128.32 (CH), 128.17 (CH), 116.24 (CH_2), 66.50 (CH_2), 43.85 (CH), 16.86 (CH_3); MS: *m/z* = 190 (M^+ , 1), 91 (Bn, 100); HR-MS: *m/z* = 191.1067, calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_2$: 191.1067; the *ee* was determined by chiral HPLC analysis (column: Chiralcel-OB-H, 98:2 heptane:*i*-PrOH); retention times (min): 11.2 (*R*-enantiomer), 11.6 (*S*-enantiomer); traces of $\text{S}_{\text{N}}2$ product (<5%) were found using NMR.

General Procedure for the Reduction of Terminal β,γ -Unsaturated Esters^[21]

In a round-bottom flask equipped with stirring bar under an O_2 atmosphere the substrate (1 equiv.) was dissolved in EtOH (6 mLmmol^{-1} substrate). A solution of catalyst **9**^[21] (20 mol%) in EtOH (1.4 mLmmol^{-1} substrate) and a solution of hydrazine hydrate (10 equiv.) in EtOH (to match with amount of catalyst solution) were added simultaneously with syringe pumps over 1 h under vigorous stirring and the reaction was vigorously stirred for another 1 h. Subsequently the reaction mixture was extracted with pentane ($4 \times 10 \text{ mLmmol}^{-1}$ substrate) and the organic layers were washed with brine, dried and concentrated to a yellow oil. Flash column chromatography (Et_2O :pentane 3:97) afforded the product.

Benzyl (S)-2-methylbutanoate (10): data in accordance with data described in ref.^[49]; colorless oil, yield (0.5 mmol scale): 91%, >95% *ee*; HR-MS: *m/z* = 215.1038, calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_2\text{Na}$: 215.1048; $[\alpha]_{\text{D}}^{20}$: +10.0 (*c* 1.0, CHCl_3), (*S*)-enantiomer; lit.^[50] value for 1.7% *ee* $[\alpha]_{\text{D}}^{20}$: +0.20 (*c* 1.87, CHCl_3), (*S*)-enantiomer. The *ee* was determined by chiral HPLC analysis (column: Chiralcel-OB-H, 99:1 heptane:*i*-PrOH); retention times (min): 10.6 (*R*)-enantiomer, 10.9 (*S*)-enantiomer.

General Procedure for the Deprotection of Benzyl Esters

In a dried Schlenk equipped with stirring bar and septum under a N_2 atmosphere the substrate was dissolved in anhydrous CH_2Cl_2 (3 mLmmol^{-1} substrate). Then the solution was cooled to -78°C and BBr_3 (1.0 M solution in CH_2Cl_2 , Aldrich, 1.5 equiv.) was added. The reaction mixture was stirred for 10 min at -78°C and was then transferred to an ice bath (0°C). After additional stirring for 1.5 h the reaction was quenched by careful addition of ice at 0°C followed by water (2.0 mLmmol^{-1} substrate). The aqueous layer was acidified by addition of a saturated aqueous solution of KHSO_4 (5 mLmmol^{-1} substrate) and the aqueous layer was extracted with CH_2Cl_2 ($3 \times 5 \text{ mLmmol}^{-1}$ substrate). Then the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography afforded the product; yield (1.0 mmol scale): 85%, 94% *ee*, colorless oil.

(S)-2-Methylbut-3-enoic acid (11): data in accordance with data described in ref.^[51] Purified by flash column chromatography (Et_2O :pentane 1:10). $[\alpha]_{\text{D}}^{20}$: +32.1 (*c* 1.0, CH_2Cl_2) The *ee* was determined by chiral GC analysis (column: Chiraldex-B-PM, 50°C to 90°C in 4 min, 90°C for 40 min, 90°C to 160°C in 7 min): retention times (min): 46.7 (*R*)-enantiomer, 48.0 (*S*)-enantiomer, 48.7 isomerized product.

General Procedure for the Hydroboration, Followed by Oxidation of β,γ -Unsaturated Esters^[52]

In a dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, the substrate (1.0 equiv.) was dissolved in anhydrous THF (1 mLmmol^{-1} substrate) and cooled to 0°C and 9-BBN-THF (Aldrich, 0.5 M solution in THF, 2.5 equiv.) was added dropwise. The reaction mixture was stirred for 1.5 h at room temperature and subsequently EtOH (3.5 equiv.) was added to destroy the excess of 9-BBN. Subsequently a pH 7 potassium phosphate buffer (4 mLmmol^{-1} substrate) and H_2O_2 (30% solution in H_2O , 4 mLmmol^{-1} substrate, ~4.7 equiv.) were added dropwise at 0°C . The reaction mixture was then allowed to warm up to room temperature and stirred for 1 h. Then the remaining peroxide was quenched at 0°C by slow addition of a saturated aqueous solution of NaHSO_3 (10 mLmmol^{-1} substrate) at 0°C . The layers were separated and the aqueous layer was washed with Et_2O ($3 \times 20 \text{ mLmmol}^{-1}$ substrate). The combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et_2O :pentane 1:4) afforded the product as a colorless oil.

Benzyl (S)-4-hydroxy-2-methylbutanoate (12): yield (0.5 mmol scale): 81%, 98% *ee*. ^1H NMR: δ = 8.59 (s, br, 1H), 7.39–7.25 (m, 5H), 5.10 (s, 2H), 3.64 (ddd, *J* = 6.3 Hz, 4.2 Hz, 1.8 Hz, 2H), 2.73–2.62 (m, 1H), 1.99–1.88 (m, 1H), 1.74–1.63 (m, 1H), 1.19 (dd, *J* = 7.1 Hz, 1.3 Hz, 3H); ^{13}C NMR: δ = 176.91 (C), 136.13 (C), 128.71 (CH), 128.36 (CH), 128.23 (CH), 66.47 (CH_2), 60.61 (CH_2), 36.65 (CH), 36.39 (CH_2), 17.27 (CH_3); MS: *m/z* = 207 ($\text{M}-\text{H}^+$, 1), 91 (Bn, 100); HR-MS: *m/z* = 231.0986, calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{Na}$: 231.0992; $[\alpha]_{\text{D}}^{20}$: +11.7 (*c* 1.0, CH_2Cl_2). The *ee* was determined by chiral HPLC analysis (column: Chiralcel-AS-H, 95:5 heptane:*i*-PrOH); retention times (min): 14.6 (*R*)-enantiomer, 15.8 (*S*)-enantiomer.

General Procedure for the Cross Metathesis (CM) of β,γ -Unsaturated Esters^[53]

In a dried Schlenk tube equipped with septum and stirring bar under a N₂ atmosphere the corresponding catalyst (5.0 mol%) and dichlorobenzoquinone (10 mol%) were dissolved in anhydrous CH₂Cl₂ (4.0 mL mmol⁻¹ substrate). After stirring for 2 min a mixture of both the substrate (1.0 equiv.) and the terminal alkene (1.2–2.0 equiv.) was added. Then a reflux condenser under a N₂ atmosphere was placed on the Schlenk tube and the mixture was refluxed for the indicated time. Then the reaction mixture was quenched with ethyl vinyl ether (1.0 mL mmol⁻¹ substrate) and stirred for 10 min. Subsequently the reaction mixture was concentrated to a yellow oil. Flash column chromatography afforded the product.

Benzyl (S,E)-2-methyldec-3-enoate (14a): purified by flash chromatography (Et₂O:pentane gradient 1:100 to 1:50); yield (3.0 mmol scale, 8 h reaction time): 84%; yield (1.0 mmol scale, 8 h reaction time): 74%; colorless oil. ¹H NMR: δ = 7.37–7.28 (m, 5H), 5.58–5.44 (m, 2H), 5.11 (s, 2H), 3.18–3.09 (m, 1H), 2.03–1.94 (m, 2H), 1.34–1.21 (m, 11H), 0.87 (t, J = 6.8 Hz, 3H); ¹³C NMR: δ = 175.11 (C), 136.37 (C), 132.75 (CH), 128.74 (CH), 128.69 (CH), 128.27 (CH), 128.12 (CH), 66.34 (CH₂), 43.08 (CH), 32.62 (CH₂), 31.89 (CH₂), 29.35 (CH₂), 28.97 (CH₂), 22.81 (CH₂), 17.64 (CH₃), 14.30 (CH₃); MS: m/z = 274 (M⁺, 1), 91 (Bn, 100), 83 (C₃H₇O, 33), 55 (C₃H₃O, 38); HR-MS: m/z = 297.1822, calcd. for C₁₈H₂₆O₂Na: 297.1831; [α]_D²⁰: +33.8 (c 1.0, CH₂Cl₂).

Benzyl (S,E)-8-(tert-butyldiphenylsilyloxy)-2-methyloct-3-enoate (14c): purified by flash chromatography (Et₂O:pentane 1:50); yield (0.5 mmol scale, 8 h reaction time): 66%; colorless oil. ¹H NMR: δ = 7.66 (dd, J = 7.8 Hz, 1.6 Hz, 4H), 7.45–7.25 (m, 11H), 5.58–5.44 (m, 2H), 5.11 (s, 2H), 3.68–3.60 (m, 2H), 3.20–3.09 (m, 1H), 1.99 (dd, J = 12.5 Hz, 7.2 Hz, 2H), 1.58–1.50 (m, 2H), 1.48–1.37 (m, 2H), 1.25 (dd, J = 7.0 Hz, 1.1 Hz, 3H), 1.04 (s, 9H); ¹³C NMR: δ = 175.06 (C), 136.34 (C), 135.77 (CH), 134.28 (C), 132.48 (CH), 129.72 (CH), 129.00 (CH), 128.70 (CH), 128.28 (CH), 128.16 (CH), 127.79 (CH), 66.37 (CH₂), 63.94 (CH₂), 43.07 (CH), 32.29 (CH₂), 32.17 (CH₂), 27.08 (CH₃), 25.60 (CH₂), 19.43 (C), 17.65 (CH₃); MS: m/z = 405 (1), 207 (C₁₁H₁₅O₂Si, 75), 91 (Bn, 100), 78 (C₆H₆, 29); HR-MS: m/z = 523.2622, calcd. for C₃₂H₄₀O₃SiNa: 523.2644; [α]_D²⁰: +17.6 (c = 1.0, CH₂Cl₂).

Benzyl (S,E)-5-bromo-2-methylpent-3-enoate (14d): purified by flash chromatography (Et₂O:pentane gradient 1:200 to 1:50); yield: (2.5 mmol scale, 24 h reaction time, 1,4-dibromobutene was used as alkene): 73%, 96% *ee*; colorless oil.^[54] ¹H NMR: δ = 7.40–7.27 (m, 5H), 5.92–5.73 (m, 2H), 5.12 (s, 2H), 3.92 (dd, J = 7.2 Hz, 0.6 Hz, 2H), 3.27–3.17 (m, 1H), 1.29 (d, J = 7.1 Hz, 3H); ¹³C NMR: δ = 173.91 (C), 135.98 (C), 134.06 (CH), 128.74 (CH), 128.40 (CH), 128.19 (CH), 128.10 (CH), 66.69 (CH₂, t, J 6.4), 42.43 (CH), 32.38 (CH₂), 17.06 (CH₃); MS: m/z = 284 (M⁺[⁸¹Br], 1), 282 (M⁺[⁷⁹Br], 1), 91 (Bn, 100); HR-MS: m/z = 305.0144, calcd. for C₁₃H₁₅⁷⁹BrO₂Na: 305.0153; [α]_D²⁰: +26.1 (c 1.0, CH₂Cl₂). The *ee* was determined by chiral HPLC analysis (column: Chiralcel-OJ-H, 99:1 heptane:*i*-PrOH): retention times (min): 31.2 (R)-enantiomer, 33.5 (S)-enantiomer.

Synthesis of *tert*-Butyl(hex-5-enyloxy)diphenylsilane

In a dried Schlenk tube equipped with septum and stirring bar under a N₂ atmosphere, the substrate (1.0 equiv.) and TBDPSCI (1.1 equiv.) were dissolved in anhydrous THF (5 mL mmol⁻¹ substrate) at room temperature. The solution was cooled to 0°C and imidazole (1 equiv.) was added. The cloudy mixture was stirred for 16 h. Then the reaction was quenched with an aqueous HCl solution (4M, 5 mL mmol⁻¹ substrate). Et₂O (20 mL mmol⁻¹ substrate) was added, and the aqueous layer was extracted with Et₂O (1 × 20 mL mmol⁻¹ substrate). Then the combined organic extracts were washed with a saturated aqueous NaHCO₃ solution (20 mL mmol⁻¹ substrate) and brine (20 mL mmol⁻¹ substrate). The combined organic layers were dried and carefully concentrated to a yellow oil. Flash column chromatography afforded the product as a colorless oil (Et₂O:pentane 1:20); yield (1.5 mmol scale): 81% yield. ¹H NMR: δ = 7.83–7.77 (m, 4H), 7.63–7.32 (m, 6H), 5.90 (ddt, J = 16.9 Hz, 10.2 Hz, 6.6 Hz, 1H), 5.19–4.94 (m, 2H), 3.79 (t, J = 6.3 Hz, 2H), 2.22–2.07 (m, 2H), 1.76–1.53 (m, 4H), 1.18 (s, 9H); ¹³C NMR: δ = 139.06 (CH), 135.78 (CH), 134.29 (C), 129.73 (CH), 127.81 (CH), 114.62 (CH₂), 63.97 (CH₂), 33.70 (CH₃), 32.24 (CH₃), 27.11 (CH₂), 25.35 (CH₃), 19.45 (CH₃); MS: m/z = 281 (M⁺–*t*-Bu, 74), 199 (C₁₂H₁₁OSi, 100), 183 (C₁₂H₁₁Si, 43); HR-MS: m/z = 339.2136, calcd. for C₂₂H₃₁OSi: 339.2144.

General Procedure for the Reduction of Internal β,γ -Unsaturated Esters

In a round-bottom flask equipped with stirring bar under an O₂ atmosphere the substrate (1 equiv.) was dissolved in EtOH (8 mL mmol⁻¹ substrate). A solution of catalyst **9**^[21] (1 equiv.) in EtOH (8 mL mmol⁻¹ substrate) and a solution of hydrazine hydrate (50 equiv.) in EtOH (to match with amount of catalyst solution) were added simultaneously by syringe pumps over 6 h under vigorous stirring and the reaction was vigorously stirred for another 1 h. During the reaction the flask was occasionally purged with O₂ (2 × every h) to remove the formed N₂ gas. Subsequently the reaction mixture was extracted with pentane (4 × 10 mL mmol⁻¹ substrate) and the organic layers were washed with brine, dried and concentrated to a yellow oil. Flash column chromatography (Et₂O: pentane 3:97) afforded the product as a colorless oil.

Benzyl (S)-2-methyldecanoate (15): yield (0.25 mmol scale) 75%, 89% conversion. ¹H NMR: δ = 7.41–7.29 (m, 5H), 5.12 (s, 2H), 2.53–2.45 (m, 1H), 1.73–1.60 (m, 1H), 1.48–1.36 (m, 1H), 1.36–1.19 (m, 12H), 1.16 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H), residual peaks from the starting material: 5.58–5.44 (2H, m), 3.18–3.13 (m, 2H), 2.03–1.96 (m, 2H); ¹³C NMR: δ = 176.90 (C), 136.43 (C), 132.70 (CH), 128.66 (CH), 128.20 (CH), 66.08 (CH₂), 39.71 (CH), 33.97 (CH₂), 32.01 (CH₂), 29.65 (CH₂), 29.59 (CH₂), 29.38 (CH₂), 27.33 (CH₂), 22.81 (CH₂), 17.20 (CH₃), 14.26 (CH₃), residual peaks from the starting material: 43.03 (CH), 32.56 (CH₂), 31.84 (CH₂), 28.92 (CH₂), 17.58 (CH₃); MS: m/z = 276 (M⁺, 1), 91 (Bn, 100), 57 (C₄H₉, 20); HR-MS: m/z = 299.1976, calcd. for C₁₈H₂₈O₂Na: 299.1982; [α]_D²⁰: +14.9 [c 0.8, CH₂Cl₂, sample contains traces of (S,E)-benzyl 2-methyldec-3-enoate].

Procedure for the Diastereoselective Cuprate Addition to Benzyl (*S,E*)-5-Bromo 2-methylpent-3-enoate (14d)

In a dried Schlenk tube equipped with septum and stirring bar under a N₂ atmosphere, CuCN (2.0 equiv.) was dissolved in anhydrous Et₂O (4 mL mmol⁻¹ substrate) and MeMgBr (Aldrich, 3.0M solution in Et₂O, 2.0 equiv.) was added. After 5 min stirring at room temperature the mixture was cooled to -40 °C and anhydrous CH₂Cl₂ (4 mL mmol⁻¹ substrate) was added. Then a solution of substrate (1.0 equiv.) in anhydrous CH₂Cl₂ (additional 2.0 mL mmol⁻¹ substrate) was added by syringe pump over 2 h. The reaction mixture was stirred for 16 h at -40 °C and subsequently EtOH (0.4 mL mmol⁻¹ substrate) and an aqueous NH₄Cl solution (1 M, 2.0 mL mmol⁻¹ substrate) were added. The mixture was warmed to room temperature and an additional 10 mL mmol⁻¹ substrate of the NH₄Cl solution and 10 mL mmol⁻¹ substrate of CH₂Cl₂ were added and the layers were separated. After extraction with CH₂Cl₂ (2 × 10 mL mmol⁻¹ substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et₂O: pentane 1:99) afforded the product as a colorless oil.

Benzyl (2*S*,3*S*)-2,3-dimethylpent-4-enoate (16): yield (0.25 mmol scale): 80%, 87:13 S_N2:S_N2'. ¹H NMR: δ = 7.44–7.28 (m, 5H), 5.70–5.57 (m, 2H), 5.13 (d, *J* = 2.2 Hz, 2H), 5.06–4.98 (m, 2H), 2.53–2.33 (m, 2H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H); ¹³C NMR: δ = 175.92 (C), 140.90 (CH), 136.25 (C), 128.64 (CH), 128.32 (CH), 128.30 (CH), 115.28 (CH₂), 66.21 (CH₂), 45.14 (CH), 41.26 (CH), 18.53 (CH₃), 14.68 (CH₃); MS: *m/z* = 218 (M⁺, 1), 91 (Bn, 100), 55 (C₃H₃O, 20); HR-MS: *m/z* = 241.1196, calcd. for C₁₄H₁₈O₂Na 241.1199; [α]_D²⁰: -4.9 [c 1.0, CH₂Cl₂, sample contains traces of benzyl (*S,E*)-2-methylhex-3-enoate].

General Procedure for the Sharpless Asymmetric *cis*-Dihydroxylation of β,γ-Unsaturated Esters^[55]

In a Schlenk tube equipped with septum and stirring bar K₃Fe(CN)₆ (3 equiv.), K₂CO₃ (3 equiv.), K₂OsO₂(OH)₄ (1.0 mol%) and methanesulfonamide (1 equiv.) were dissolved in H₂O (5 mL mmol⁻¹ substrate) then the corresponding ligand (2.5 mol%) was added followed by *t*-BuOH (4 mL mmol⁻¹ substrate). The solution was cooled to 0 °C and the substrate (1 equiv.) in *t*-BuOH (additional 1 mL mmol⁻¹ substrate) was added dropwise. The mixture was stirred for 16 h. Then a saturated aqueous NaHSO₃ solution (1 mL mmol⁻¹ substrate) was slowly added and the suspension was warmed to room temperature with vigorous stirring. MeOAc (20 mL mmol⁻¹ substrate) was added, and the aqueous layer was extracted with MeOAc (5 × 20 mL mmol⁻¹ substrate). Then the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (gradient pentane:Et₂O 1:1 to Et₂O) afforded the product as a colorless oil.

(3*S*,4*S*)-4-Hydroxy-3-methyldihydrofuran-2(3*H*)-one [(3*S*,4*S*)-18]: data in accordance with data described in ref.^[56]; yield: (0.5 mmol scale): 61%; colorless oil; high *ee* (see Supporting Information for spectra); [α]_D²⁰: -67.9 (c 1.0, CHCl₃); lit.^[34a] value [α]_D²⁰: (c 2.0, CHCl₃), (3*R*,4*R*)-enantiomer. The *ee* was determined by chiral GC analysis

(column: Chiraldex-G-TA, 50 °C to 105 °C in 5.5 min; 105 °C for 120 min, 105 °C to 170 °C for 32.5 min); retention times (min): 127.7 (*R,R*)-enantiomer, 131.3 (*S,S*)-enantiomer.

(3*R*,4*S*)-4-Hydroxy-3-methyldihydrofuran-2(3*H*)-one [(3*R*,4*S*)-18]: data in accordance with data described in ref.^[57]; yield (0.5 mmol scale): 46%; colorless oil; 98% *ee*; [α]_D²⁰: -26.0 [c 0.5, CHCl₃, sample contains traces of methanesulfonamide]; lit.^[34a] value [α]_D²⁰: +6.82 (c 2.2, CHCl₃), (3*S*,4*R*)-enantiomer. The *ee* was determined by chiral GC analysis (column: Chiraldex-G-TA, 50 °C to 130 °C in 8 min, 130 °C for 40 min, 130 °C to 170 °C in 20 min); retention times (min): 50.0 (*S,R*)-enantiomer, 54.0 (*R,S*)-enantiomer.

General Procedure for the Iodolactonization of β,γ-Unsaturated Esters with a Terminal Olefin towards 5-Membered Lactones

In a Schlenk tube equipped with stirring bar and septum under a N₂ atmosphere, (bipyridine)iodonium tetrafluoroborate (1.1 equiv.) was dissolved in CH₂Cl₂ (20 mL mmol⁻¹ substrate). The reaction mixture was cooled to -78 °C and HBF₄ (54% in Et₂O, 1.5 equiv.) was added whereupon the solution turned pink. Then the substrate dissolved in CH₂Cl₂ (10 mL mmol⁻¹ substrate) was added slowly. After stirring for 1.5 h (-78 °C to -10 °C) the reaction was quenched with an aqueous Na₂S₂O₃ solution (20 mL mmol⁻¹ substrate) and extracted by CH₂Cl₂ (2 × 10 mL mmol⁻¹ substrate). Then the combined organic extracts were washed with water (2 × 10 mL mmol⁻¹ substrate) dried and carefully concentrated to a yellow oil. Flash column chromatography (gradient Et₂O: pentane 1:49 to 2:23) afforded the product.

(3*R*,4*S*)-4-Iodo-3-methyldihydrofuran-2(3*H*)-one (19): yield (0.25 mmol scale): 27%; 96% *ee*; colorless oil. ¹H NMR: δ = 4.61 (dd, *J* = 9.4 Hz, 7.3 Hz, 1H), 4.38 (dd, *J* = 10.0 Hz, 9.4 Hz, 1H), 4.05–3.95 (m, 1H), 2.73 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 1.34 (d, *J* = 7.1 Hz, 3H); ¹³C NMR: δ = 176.00 (C), 73.97 (CH), 45.56 (CH₂), 17.40 (CH), 12.59 (CH₃); MS: *m/z* = 226 (M⁺, 14), 127 (I⁺, 19), 99 (M⁺-I, 32), 71 (C₃H₃O₂, 26), 55 (C₃H₃O, 100); HR-MS: *m/z* = 226.9562, calcd. for C₅H₈IO₂: 226.9563; [α]_D²⁰: -16.9 (c 1.0, CH₂Cl₂). The *ee* was determined by chiral GC analysis (column: ChiralDEX-CB, 50 °C for 5 min, 50 °C to 80 °C in 6 min, 80 °C for 20 min, 80 °C to 180 °C in 20 min); retention times (min): 44.8 (*R,S*)-enantiomer, 45.0 (*S,R*)-enantiomer.

General Procedure for the Iodolactonization of β,γ-Unsaturated Esters with a Terminal Olefin towards 4-Membered Lactones

In a Schlenk tube equipped with septum and stirring bar under a N₂ atmosphere, I₂ (5 equiv.) and K₃PO₄ (5 equiv.) were dissolved in anhydrous CH₂Cl₂ (100 mL mmol⁻¹ substrate). Then the substrate (1 equiv.) in anhydrous CH₂Cl₂ (5 mL mmol⁻¹ substrate) was added dropwise. After stirring for 40 h the reaction mixture was quenched with a saturated aqueous Na₂S₂O₃ solution (50 mL mmol⁻¹ substrate). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 50 mL mmol⁻¹ substrate). Then the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (gradient Et₂O: pentane 1:49 to 2:23) afforded the product.

(3*S*,4*R*)-4-(Iodomethyl)-3-methyloxetan-2-one (20): yield (0.25 mmol scale): 47% yield; 97% *ee*; colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 4.40–4.26 (m, 1H), 3.54 (dd, *J* = 10.0 Hz, 4.8 Hz, 1H), 3.45–3.35 (m, 1H), 3.31 (t, *J* = 9.7 Hz, 1H), 1.47 (d, *J* = 7.5 Hz, 3H); ¹³C NMR: δ = 170.11 (C), 77.13 (CH), 53.28 (CH), 12.90 (CH₃), 3.78 (CH₂); MS: *m/z* = 226 (M⁺, 1), 127 (I⁺, 15), 56 (C₃H₃O, 13), 55 (C₃H₃O, 100); HR-MS: *m/z* = 226.9563, calcd. for C₅H₈IO₂: 226.9563; [α]_D²⁰: +19.2 [*c* 1.0, CH₂Cl₂, sample contains traces of (3*R*,4*S*)-4-iodo-3-methyldihydrofuran-2(3*H*)-one]. The *ee* was determined by chiral GC analysis (column: Chiralsil DEX-CB, 50°C for 5 min, 50°C to 80°C in 6 min, 80°C for 20 min, 80°C to 180°C in 20 min); retention times (min): 44.3 (*R,S*)-enantiomer, 44.6 (*S,R*)-enantiomer, 44.8 (*R,S*)-enantiomer of 5-membered lactone.

(*S,E*)-2-Methyldec-3-enoic acid (21): prepared via the general procedure for the deprotection of benzyl esters and purified by flash column chromatography (pentane:Et₂O 10:1); yield (0.3 mmol scale): 84%; colorless oil. ¹H NMR: δ = 5.74–5.41 (m, 2H), 3.19–3.07 (m, 1H), 2.02 (dd, *J* = 6.7 Hz, 2H), 1.43–1.19 (m, 11H), 0.88 (t, *J* = 6.6 Hz, 3H); ¹³C NMR: δ = 181.29 (C), 133.18 (CH), 128.08 (CH), 42.81 (CH), 32.56 (CH₂), 31.82 (CH₂), 29.24 (CH₂), 28.94 (CH₂), 22.76 (CH₂), 17.43 (CH₃), 14.23 (CH₃); MS: *m/z* = 184 (M⁺, 1), 74 (72), 69 (C₄H₅O, 98), 55 (C₃H₃O, 100); HR-MS: *m/z* = 185.1533, calcd. for C₁₁H₂₁O₂: 185.1536; [α]_D²⁰: +42.2 (*c* 1.0, CH₂Cl₂).

General Procedure for the Iodolactonization of β,γ -Unsaturated Esters with an Internal Olefin

In a Schlenk tube equipped with stirring bar and septum under a N₂ atmosphere, bis(pyridine)iodonium tetrafluoroborate (1.1 equiv.) was dissolved in CH₂Cl₂ (20 mL mmol^{−1} substrate). The reaction mixture was cooled to −78°C and HBF₄ (54% in Et₂O, 1.5 equiv.) was added whereupon the solution turned pink. Then the substrate dissolved in CH₂Cl₂ (10 mL mmol^{−1} substrate) was added slowly. After stirring for 1.5 h (−78°C to −10°C) the reaction was quenched with an aqueous Na₂S₂O₃ solution (20 mL mmol^{−1} substrate) and extracted by CH₂Cl₂ (2 × 10 mL mmol^{−1} substrate). Then the combined organic extracts were washed with water (2 × 10 mL mmol^{−1} substrate), dried and carefully concentrated to a yellow oil. Flash column chromatography (gradient Et₂O:pentane 1:49 to 2:23) afforded the product.

(3*R*,4*S*,5*R*)-5-Hexyl-4-iodo-3-methyldihydrofuran-2(3*H*)-one (22): yield (0.25 mmol scale): 65%; colorless oil. ¹H NMR: δ = 4.51 (ddd, *J* = 9.8 Hz, 8.5 Hz, 2.9 Hz, 1H), 3.60 (dd, *J* = 11.7 Hz, 9.9 Hz, 1H), 2.80 (dq, *J* = 11.8 Hz, 7.1 Hz, 1H), 2.02–1.88 (m, 1H), 1.66–1.18 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 3H); ¹³C NMR: δ = 175.42 (C), 85.93 (CH), 47.02 (CH), 32.17 (CH₂), 31.67 (CH₂), 29.00 (CH₂), 25.49 (CH₂), 25.13 (CH), 22.65 (CH₂), 14.19 (CH₃), 12.50 (CH₃); MS: *m/z* = 225 (M⁺–hexyl, 3), 109 (C₇H₉O, 32), 109 (C₆H₉O, 33), 83 (C₅H₇O, 58), 69 (C₄H₅O, 57), 55 (C₃H₃O, 100); HR-MS: *m/z* = 311.0501, calcd. for C₁₁H₁₂IO₂: 311.0503; [α]_D²⁰: +41.9 (*c* 1.0, CH₂Cl₂).

Synthesis of Racemic Benzyl 2-Methylbut-3-enoate (6a)

The synthesis of racemic 2-methylbut-3-enoic acid (**11**) was performed via the procedure described in ref.^[57] but omitting the addition of BnBr. The crude product was used to prepare benzyl 2-methylbut-3-enoate **6a** via the general procedure for the esterification of 4-bromocrotonic acid; yield 38% (over 2 steps). For experimental data *vide supra*.

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