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

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Received: February 10, 2010; Published online: April 7, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000109.

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 (vinyl 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_{2}2’ addition is favored over 1,4-addition, 1,2-addition and S_{2}2 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).
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 SN2'-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 (CuOTf)2·C6H6 and chiral peptidic Schiff base ligands for the AAA of a variety of di-alkylzinc reagents, tertiary [7a] and quaternary carbon centers[7b] were constructed with high regioselectivity and ee. This methodology requires the use of 6 equiv. of Me2Zn 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. This lack of application might be due to the stereocentric 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 CuBr·SMe2 at −40°C or employing either reversed JosiPhos (L2) or JosiPhos (L3) at −78°C in CH2Cl2, a mixture of Sα2 (7a) and Sα2' products (6a) was obtained (entries 1–3). However, the use of TaniaPhos (L1) gave selectively the Sα2' 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

![Figure 1](https://asc.wiley-vch.de/.../C23 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim)

![Figure 2](https://asc.wiley-vch.de/.../C23 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim)

**Table 1.** Ligand screening for regioselective Sα2'-alkylation using MeMgBr.[4]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Lidag</th>
<th>Conversion[a]</th>
<th>6[b]</th>
<th>7[c]</th>
<th>8[d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OBn</td>
<td>none</td>
<td>full</td>
<td>50%</td>
<td>50%</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>OBn</td>
<td>L2[4]</td>
<td>93%</td>
<td>52%</td>
<td>27%</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>OBn</td>
<td>L3[4]</td>
<td>76%[d]</td>
<td>31%</td>
<td>26%</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>OBn</td>
<td>L1[4]</td>
<td>full</td>
<td>&gt;95%</td>
<td>&lt;5%</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>SET</td>
<td>L1[4]</td>
<td>full</td>
<td>49%</td>
<td>–</td>
<td>47%</td>
</tr>
</tbody>
</table>

[a] Conditions: 5a or 5b (1 equiv.) in CH2Cl2 was added to a solution of MeMgBr (3.0M in Et2O, 1.2 equiv.), ligand (1.1 mol%) and CuBr·SMe2 (1 mol%) in CH2Cl2 (0.2M 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] CuBr·SMe2 (1 equiv.) was used at −40°C.

[d] L3 (2.2 mol%) and CuBr·SMe2 (2 mol%) were used.

[e] 19% of benzylcrotonate obtained (see further ref.[14]).
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,S,2 product were observed. Performing the reaction in up to 6.6 mmol (1.7 g) scale 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).

Elaboration of the products to multifunctional building blocks proved challenging due to the ready isomerization of the $\beta$-$\gamma$-unsaturated ester to the conjugated $\alpha$,$\beta$-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 $\alpha$-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*, and the synthesis of several fragrances. We were able to reduce the olefin in high yield retaining the chiral integrity of the $\alpha$-Me center, without deprotection of the ester [Scheme 2, Eq (a)].

Table 2. AAA of MeMgBr to 5a at increasing quantity.[4]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scale</th>
<th>Reaction Time</th>
<th>Yield</th>
<th>ee[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 mmol, 0.12 g</td>
<td>2 h</td>
<td>86%</td>
<td>99%</td>
</tr>
<tr>
<td>2[c]</td>
<td>2.0 mmol, 0.51 g</td>
<td>40 h</td>
<td>81%</td>
<td>96%</td>
</tr>
<tr>
<td>3</td>
<td>2.5 mmol, 0.64 g</td>
<td>16 h</td>
<td>88%</td>
<td>98%</td>
</tr>
<tr>
<td>4</td>
<td>4.0 mmol, 1.02 g</td>
<td>16 h</td>
<td>87%</td>
<td>98%</td>
</tr>
<tr>
<td>5</td>
<td>6.6 mmol, 1.68 g</td>
<td>16 h</td>
<td>90%</td>
<td>98%</td>
</tr>
</tbody>
</table>

[a] Conditions: 5a (1 equiv.) in CH$_2$Cl$_2$ was added to a solution of MeMgBr (3.0 M in Et$_2$O, 1.2 equiv.), L1 (1.1 mol%) and CuBr·SMe$_2$ (1 mol%) in CH$_2$Cl$_2$ (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]

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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.), BBr$_3$ (1.5 equiv.), CH$_2$Cl$_2$ (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) H$_2$O$_2$ (~4.7 equiv.), phosphate buffer pH 7.0 (total THF and H$_2$O 0.13 M in 6a).
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 multistria- tin.
[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 and the synthesis of four stereoisomers of the phytophthora c1 mating hormone.
[25a] 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 3. Reduction of the β,γ-unsaturated olefin of 6a.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reduction Method</th>
<th>Hydrazine</th>
<th>Time</th>
<th>Reduction[b]</th>
<th>Isomerization[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd/C (0.25%)</td>
<td>–</td>
<td>1 h</td>
<td>full</td>
<td>24%</td>
</tr>
<tr>
<td>2</td>
<td>9 (5%)</td>
<td>20 equiv.</td>
<td>4 h</td>
<td>full</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>3</td>
<td>9 (20%)</td>
<td>10 equiv.</td>
<td>2 h</td>
<td>full</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

[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.

Table 4. Deprotection of the carboxylic acid of 6a.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Conversion[b]</th>
<th>Isomerization[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiOH</td>
<td>&gt;95%</td>
<td>53%</td>
</tr>
<tr>
<td>2</td>
<td>LiOH, LiCl, H2O2</td>
<td>78%</td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td>TFA</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>4</td>
<td>BBr3</td>
<td>&gt;95%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

[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.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of 9-BBN</th>
<th>Conversion[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>traces</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>3%</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

[a] Conditions: 6a (1 equiv.), 9-BBN (0.5 M solution in THF), 0°C, 5 h.
[b] Conversion from (S)-6a to (S)-13 was determined by GC-MS.
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 \(\alpha\)-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 \(\alpha\)-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 \(anti\)-vician dimethyl motifs,\[34d,32\] 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 methylsulfonylamide\[15\] to speed up the dihydroxylation of 6a, ligand L5 proved superior for the preparation of the \(anti\)-\(\beta\)-hydroxy-\(\gamma\)-butyrolactone (entry 2) and L6 gave the best results for the \(syn\)-\(\beta\)-hydroxy-\(\gamma\)-butyrolactone

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Conversion[b]</th>
<th>Isomerization[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs I</td>
<td>–</td>
<td>62%</td>
<td>86%</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs II</td>
<td>–</td>
<td>92%</td>
<td>27%</td>
</tr>
<tr>
<td>3</td>
<td>Hoveyda-Grubbs I</td>
<td>–</td>
<td>68%</td>
<td>3%</td>
</tr>
<tr>
<td>4</td>
<td>Hoveyda-Grubbs II</td>
<td>–</td>
<td>full</td>
<td>76%</td>
</tr>
<tr>
<td>5</td>
<td>Hoveyda-Grubbs II</td>
<td>Cl2BQ</td>
<td>full</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

\[a\] Conditions: 6a (1 equiv.), 1-octene (2 equiv.), catalyst (5 mol%), 2,6-dichlorobenzoquinone (10 mol%), CH\(_2\)Cl\(_2\) (0.25M in 6a), 40°C, 16 h.

\[b\] Conversion and isomerization were determined by GC-MS and correlate with the ratio observed by \(^1\)H NMR.
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 \((\text{S})\)-\(\text{a}\)-multistriatin\[33c\] and apoptolidinone.\[37\] Finally, when the deprotected \(\text{b}\), \(\text{g}\)-unsaturated carboxylic acid \((\text{S})\)-\(\text{11}\) was subjected to iodolactonization using Barluenga/C29s reagent\[38,39\] the 5-membered lactone [Scheme 6, Eq. (b)] was obtained albeit in a low yield.\[40\] Performing the iodolactonization employing \(\text{I}_2\) and \(\text{K}_3\text{PO}_4\) in \(\text{CH}_2\text{Cl}_2\) 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

### Table 7. Cross metathesis of \(\text{6a}\) with a variety of olefins.\[a\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Product</th>
<th>Time</th>
<th>Yield</th>
<th>Isomerization[^{[b]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>(\text{14a})</td>
<td>8 h</td>
<td>84%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2[^{[c]}]</td>
<td></td>
<td>(\text{14b})</td>
<td>16 h</td>
<td>nd (91%)[^{[d]}]</td>
<td>91%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>(\text{14c})</td>
<td>8 h</td>
<td>66%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>(\text{14d})</td>
<td>16 h</td>
<td>73%[^{[e]}]</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Conditions: \(\text{6a}\) (1 equiv.), olefin (2 equiv.), HG-II (5 mol\%), 2,6-dichlorobenzoquinone (10 mol\%), \(\text{CH}_2\text{Cl}_2\) (0.25 M in \(\text{6a}\)), 40°C, 16 h.

\[^{[b]}\] % isomerization is determined by \(^1\text{H}\) 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 \(\alpha\)-Me-substituted esters. Conditions: see Table 7 for CM. \(\text{14a}\) (1 equiv.), \(\text{9}\) (1 equiv.), hydrazine hydrate (50 equiv.), \(\text{EtOH}\) (0.11 M in \(\text{14a}\)), room temperature, \(\text{O}_2\) 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. \(\text{14d}\) (1 equiv.), \(\text{MeMgBr}\) (2 equiv.), \(\text{CuCN}\) (2 equiv.), \(\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2\) (2.3, 0.1 M in \(\text{14d}\)), –40°C, 16 h.

### Scheme 5. Synthesis of lactonized propionate motifs. Conditions: see Table 8.
stereogenic centers by an AAA–CM–carboxylic acid deprotection–iodolactonization sequence. We managed to obtain 22 in good yield as the single 3,4-trans-4,5-trans diastereomer \cite{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 \( \alpha \)-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 K2MnO4 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/min1, 205 nm; chiralcel OB-H, 4.6 × 250 mm, 5 m, 40°C, 0.5 mL/min2, 205 nm; chiralcel OJ-H, 4.6 × 250 mm, 5 m, 40°C, 0.5 mL/min3, 205 nm) in comparison to authentic samples of racemates of the products. Optical rotations were measured in CH3Cl or CHCl3 on a Schmidt Haensch polarimeter (Polartronic MHB) with a 10 cm cell (ε given in g/100 mL). 1H NMR spectra were recorded at 400 MHz with residual solvent peaks (CHCl3, d = 7.26 ppm) using tetramethylsilane (TMS) as a reference. 13C NMR spectra were recorded in CH2Cl2 or CHCl3 on a Varian AMX400 spectrometer. 1H 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 ppm for hydrogen atoms, δ = 77.23 ppm 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 Fischer-Scientific 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. CuBr·SMe2 was purchased from Sigma-Aldrich. K2OsO2(OH)4, (DHQ)2AQN, (DHQ)2Phal and (DHQ)2Pyr Tantaphos and (R,R)-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 (CH3); MS: m/z = 166 (M+179Br), 56, 164 (M+179Br), 56, 85 (M–Br, 100); HR-MS: m/z = 163.9471, calcd. for C4H5BrO; 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.) 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.[7] MS: m/z = 256 (M+179Br)1, 254 (M+179Br)1, 175 (M–Br, 29), 156 (44), 107 (BnO, 28), 91 (Bn, 100).

Thioesterification of 4-Bromocrotonic Acid

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 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-enoate (5b): data in accordance with data described in ref.[8]

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...
Copper-Catalyzed Asymmetric Allylic Alkylation of Halocrotonates:

In a dried Schlenk equipped with septum and stirring bar under a N\textsubscript{2} atmosphere the substrate was dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (3 mL mmol\textsuperscript{-1} substrate). Then the solution was cooled to −78 \degree C and BBr\textsubscript{3} (1.0 M solution in CH\textsubscript{2}Cl\textsubscript{2}, Aldrich, 1.5 equiv.) was added. The reaction mixture was stirred for 10 min at −78 \degree C and was then transferred to an ice bath (0 \degree C). After additional stirring for 1.5 h the reaction was quenched by careful addition of ice at 0 \degree C followed by water (2.0 mL mmol\textsuperscript{-1} substrate). The aqueous layer was acidified by addition of a saturated aqueous solution of KH\textsubscript{2}SO\textsubscript{4} (5 mL mmol\textsuperscript{-1} substrate) and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 \times 5 mL mmol\textsuperscript{-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.

**General Procedure for the Deprotection of Benzyl Esters**

In a dried Schlenk tube equipped with septum and stirring bar under a N\textsubscript{2} atmosphere the substrate (1.0 equiv.) was dissolved in anhydrous THF (1 mL mmol\textsuperscript{-1} substrate) and cooled to 0 \degree 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 Et\textsubscript{2}OH (3.5 equiv.) was added to destroy the excess of 9-BBN. Subsequently a pH 7 potassium phosphate buffer (4 mL mmol\textsuperscript{-1} substrate) and H\textsubscript{2}O (30\% solution in H\textsubscript{2}O, 4 mL mmol\textsuperscript{-1} substrate − 4.7 equiv.) were added dropwise at 0 \degree 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 \degree C by slow addition of a saturated aqueous solution of Na\textsubscript{2}SO\textsubscript{4} (10 mL mmol\textsuperscript{-1} substrate) at 0 \degree C. The layers were separated and the aqueous layer was washed with Et\textsubscript{2}O (3 \times 20 mL mmol\textsuperscript{-1} substrate). The combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (Et\textsubscript{2}O:pentane 1:4) afforded the product as a colorless oil.

**Benzylic (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)-enantior: yield (2.0 mmol scale): 81\%, 96\% ee [\text{ee}^\text{R} = +19.0 (c 1.0, CH\textsubscript{3}Cl), (S)-enantior: using (S,S)-TaniaPhos [\text{ee}^\text{S} = -20.2 (c 1.0, CH\textsubscript{3}Cl)]; (R)-enantior: lit.\textsuperscript{[25]} for 10\% ee [\text{ee}^\text{R} = -1.5 (c 0.7, CH\textsubscript{3}Cl)]; (R)-enantior. \text{H NMR}: \delta = 7.38–7.25 (m, 5 H), 5.92 (dd, J = 17.5 Hz, 10.2 Hz, 7.5 Hz, 1 H), 5.17–5.04 (m, 4 H), 3.23–3.13 (m, 1 H), 2.69–2.62 (m, 1 H), 1.99–1.88 (m, 1 H), 1.74–1.63 (m, 1 H), 0.19 (s, br, 3 H); \text{13C NMR}: \delta = 174.41 (C), 137.17 (CH), 136.19 (C), 128.70 (CH), 128.32 (CH), 128.17 (CH), 116.24 (CH\textsubscript{3}), 66.50 (CH\textsubscript{2}), 43.85 (CH), 16.86 (CH\textsubscript{3}); \text{MS}: m/z = 190 (M\textsuperscript{+}, 1), 91 (M, 100); \text{HR-MS}: m/z = 191.1067, calcd. for C\textsubscript{12}H\textsubscript{15}O\textsubscript{2}: 191.1067; the ee was determined by chiral GC analysis (column: Chiraldex-B-PM, 50\% of 90 \degree C in 4 min, 90 \degree C for 40 min, 90 \degree C to 160 \degree C in 7 min): retention times (min): 46.7 (R)-enantior, 48.0 (S)-enantior, 48.7 isomerized product.

**General Procedure for the Hydroboration, Followed by Oxidation of \(\beta,\gamma\)-Unsaturated Esters**\textsuperscript{[24]}

In a round-bottom flask equipped with stirring bar under an O\textsubscript{2} atmosphere the substrate (1 equiv.) was dissolved in Et\textsubscript{2}OH (6 mL mmol\textsuperscript{-1} substrate). A solution of catalyst g[\textsuperscript{2}](20 mol\textsuperscript{-}\text{\textsuperscript{1}}) in Et\textsubscript{2}OH (1.4 mL mmol\textsuperscript{-1} substrate) and a solution of hydrazine hydrate (10 equiv.) in Et\textsubscript{2}OH (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 mL mmol\textsuperscript{-1} substrate) and the organic layers were washed with brine, dried and concentrated to a yellow oil. Flash column chromatography (Et\textsubscript{2}O:pentane 1:3) afforded the product.

**Benzylic (S)-2-methylbutanoate (10):** data in accordance with data described in ref.\textsuperscript{[26]} colorless oil, yield (0.5 mmol scale): 91\%, > 95\% ee; \text{HR-MS}: m/z = 215.1038, calcd. for C\textsubscript{9}H\textsubscript{14}O\textsubscript{2}Na: 215.1048; [\text{ee}^\text{R} = +10.0 (c 1.0, CHCl\textsubscript{3}), (S)-enantior: lit.\textsuperscript{[26]} for 1.7% ee [\text{ee}^\text{S} = +0.20 (c 1.87, CHCl\textsubscript{3})], (S)-enantior. The ee was determined by chiral HPLC analysis (column: Chiralcel-OB-H, 99:1 heptane:i-PrOH): retention times (min): 10.6 (R)-enantior, 10.9 (S)-enantior.

**Benzylic (S)-4-hydroxy-2-methylbutanoate (12):** yield (0.5 mmol scale): 81\%, > 95\% ee; \text{H NMR}: \delta = 8.59 (s, br, 1 H), 7.39–7.25 (m, 5 H), 5.10 (s, 2 H), 3.64 (dd, J = 6.3 Hz, 4.2 Hz, 1.8 Hz, 2 H), 2.73–2.62 (m, 1 H), 1.99–1.88 (m, 1 H), 1.74–1.63 (m, 1 H), 1.19 (dd, J = 7.1 Hz, 1.3 Hz, 3 H); \text{13C NMR}: \delta = 176.91 (C), 136.13 (C), 128.71 (CH), 128.36 (CH), 128.23 (CH\textsubscript{3}), 66.47 (CH\textsubscript{2}), 60.61 (CH\textsubscript{3}), 36.65 (CH), 36.39 (CH\textsubscript{2}), 17.27 (CH\textsubscript{3}); \text{MS}: m/z = 207 (M\textsuperscript{+}–H\textsubscript{\textsuperscript{1}}, 1), 91 (M, 100); \text{HR-MS}: m/z = 231.0986, calcd. for C\textsubscript{9}H\textsubscript{14}O\textsubscript{2}Na: 231.0992; [\text{ee}^\text{R} = +11.7 (c 1.0, CH\textsubscript{3}Cl)]. The ee was determined by chiral HPLC analysis (column: Chiralcel-AS-H, 95:5 heptane:i-PrOH): retention times (min): 14.6 (R)-enantior, 15.8 (S)-enantior.
General Procedure for the Cross Metathesis (CM) of \( \beta,\gamma\)-Unsaturated Esters\[^{53}\]

In a dried Schlenk tube equipped with septum and stirring bar under a \( \text{N}_2 \) atmosphere the corresponding catalyst (5.0 mol\%) and dichlorobenzozquinone (10 mol\%) were dissolved in anhydrous \( \text{CH}_2\text{Cl}_2 \) (4.0 mmol\textsuperscript{-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 \( \text{N}_2 \) atmosphere was placed on the Schlenk tube and the mixture was reflushed for the indicated time. Then the reaction mixture was quenched with ethyl vinyl ether (1.0 mmol\textsuperscript{-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-methyldecape-3-enoate (14a):** purified by flash chromatography (Et\( \text{O}_2\text{O}:\text{pentane} \) 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. \(^1\)H NMR: \( \delta = 7.37–7.28 \) (m, 5 \( \text{H} \)), 5.58–5.44 (m, 2 \( \text{H} \)), 5.11 (s, 2 \( \text{H} \)), 3.18–3.09 (m, 1 \( \text{H} \)), 2.03–1.94 (m, 2 \( \text{H} \)); 13C NMR: \( \delta = 175.93 \) (C), 135.98 (C), 134.06 (C), 128.74 (CH), 128.40 (CH), 128.19 (CH), 128.10 (CH), 66.69 (CH\(_3\), t J 6.4 Hz), 42.43 (CH), 32.38 (CH\(_2\)), 17.06 (CH\(_3\)); MS: \( m/z = 284 \) (M\(^+\)Br, 1), 282 (M\(^+\)), 244 (M\(^+\)Br, 1), 91 (Bn, 100); HR-MS: \( m/z = 297.2182 \), calcd. for \( \text{C}_{20}\text{H}_{28}\text{O}_{2}\text{Si} \): 297.2198.

**Benzyl (S,E)-8-(tert-butylidihydrobisdilysiloxy)-2-methyloct-3-enoate (14c):** purified by flash chromatography (Et\( \text{O}_2\text{O}:\text{pentane} \) gradient 1:100 to 1:50); yield (0.5 mmol scale, 8 h reaction time): 66%; colorless oil. \(^1\)H NMR: \( \delta = 7.66 \) (dd, \( J = 7.8 \) Hz, 1.6 Hz, 4 \( \text{H} \)), 7.45–7.25 (m, 11 \( \text{H} \)), 5.58–5.44 (m, 2 \( \text{H} \)), 5.11 (s, 2 \( \text{H} \)), 3.68–3.60 (m, 2 \( \text{H} \)), 3.20–3.09 (m, 1 \( \text{H} \)), 1.99 (dd, \( J = 12.5 \) Hz, 7.2 Hz, 2 \( \text{H} \)), 1.58–1.50 (m, 2 \( \text{H} \)), 1.48–1.37 (m, 2 \( \text{H} \)), 1.25 (dd, \( J = 7.0 \) Hz, 1.1 Hz, 3 \( \text{H} \)), 1.04 (s, 9 \( \text{H} \)); 13C NMR: \( \delta = 178.04 \) (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 (CH\(_3\)), 63.94 (CH), 43.07 (CH), 32.29 (CH), 32.17 (CH), 27.08 (CH), 25.60 (CH), 19.43 (C), 17.65 (CH\(_3\)); MS: \( m/z = 405 \) (1), 207 (M\(^+\)C\(_5\)H\(_7\)O, 33), 176 (M\(^+\)) \( \text{Si} \), 173 (M\(^+\)C\(_5\)H\(_7\)O), 106 (C\(_9\)H\(_9\)O, 38); HR-MS: \( m/z = 405.0144 \), calcd. for \( \text{C}_{23}\text{H}_{20}\text{O}_{2}\text{Si} \): 405.0144.

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

In a dried Schlenk tube equipped with septum and stirring bar under a \( \text{N}_2 \) atmosphere, the substrate (1.0 equiv) and TBDPSCl (1.1 equiv) were dissolved in anhydrous THF (5 mmol\textsuperscript{-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 mmol\textsuperscript{-1} substrate). Et\( \text{O} \) (20 mmol\textsuperscript{-1} substrate) was added, and the aqueous layer was extracted with Et\( \text{O} \) (1 \( \times \) 20 mmol\textsuperscript{-1} substrate). Then the combined organic extracts were washed with a saturated aqueous NaHCO\(_3\) solution (20 mmol\textsuperscript{-1} substrate) and brine (20 mmol\textsuperscript{-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 (Et\( \text{O}_2\text{O}:\text{pentane} \) 1:20); yield (1.5 mmol scale): 81% yield. \(^1\)H NMR: \( \delta = 7.83–7.77 \) (m, 4 \( \text{H} \)), 7.63–7.32 (m, 6 \( \text{H} \)), 5.90 (ddt, \( J = 16.9 \) Hz, \( J = 6.6 \) Hz, 6.6 Hz, 1 \( \text{H} \)), 5.19–4.94 (m, 2 \( \text{H} \)), 3.79 (t, \( J = 6.3 \) Hz, 2 \( \text{H} \)), 2.22–2.07 (m, 2 \( \text{H} \)), 1.76–1.53 (m, 4 \( \text{H} \)), 1.18 (s, 9 \( \text{H} \)); 13C NMR: \( \delta = 139.06 \) (CH), 135.78 (CH), 134.29 (C), 129.73 (CH), 127.81 (CH), 114.62 (CH\(_3\)), 63.97 (CH\(_3\)), 33.70 (CH\(_3\)), 32.24 (CH), 27.11 (CH\(_3\)), 25.35 (CH\(_3\)), 19.45 (CH\(_3\)); MS: \( m/z = 281 \) (M\(^+\)-t-Bu, 74), 199 (C\(_9\)H\(_{13}\)O\(_2\)Si, 100), 183 (C\(_8\)H\(_{14}\)Si, 43); HR-MS: \( m/z = 281.5855 \), calcd. for \( \text{C}_{20}\text{H}_{28}\text{O}_{2}\text{Si} \): 281.5864.

General Procedure for the Reduction of Internal \( \beta,\gamma\)-Unsaturated Esters

In a round-bottom flask equipped with stirring bar under an \( \text{O}_2 \) atmosphere the substrate (1 equiv.) was dissolved in Et\( \text{O} \) (8 mmol\textsuperscript{-1} substrate). A solution of catalyst 9\[^{21}\] (1 equiv.) in Et\( \text{O} \) (8 mmol\textsuperscript{-1} substrate) and a solution of hydrazine hydrate (50 equiv.) in Et\( \text{O} \) (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 \( \text{O}_2 \) (2 x every h) to remove the formed \( \text{N}_2 \) gas. Subsequently the reaction mixture was extracted with pentane (4 x 10 mmol\textsuperscript{-1} substrate) and the organic layers were washed with brine, dried and concentrated to a yellow oil. Flash column chromatography (Et\( \text{O} \): pentane 1:50) afforded the product as a colorless oil.
Copper-Catalyzed Asymmetric Allylic Alkylation of Halocrotonates:

Procedure for the Diastereoselective Cuprate Addition to Benzyl (S,E)-5-Bromo 2-methylpent-3-enolate (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, 3.0 M 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 (2S,3S)-2,3-dimethylpent-4-enolate (16): yield (0.25 mmol scale): 80%; 87:13 S:N2:SN2. 1H NMR: δ = 7.44–7.28 (m, 5H), 5.70–5.57 (m, 2H), 5.13 (d, J = 1.2 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 (C), 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 (C₅H₅O, 20); HR-MS: m/z calculated for C₁₃H₂₂O₂Na 241.1196; calcd. for C₁₃H₂₂O₂Na 241.1199; [α]D²⁰ = −4.9 [c 1.0, CHCl₃, sample contains traces of benzyl (S,E)-2-methylhex-3-enolate).

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

In a Schlenk tube equipped with septum and stirring bar K₂Fe(CN)₄ (3 equiv.), K₂CO₃ (3 equiv.), K₂OsO₂(OH)₄ (1.0 mol%) and methanesulfonamide (1 equiv.) were dissolved in anhydrous CH₂Cl₂ (20 mL mmol⁻¹ substrate). K₃Fe(CN)₆ (3 equiv.), K₂CO₃ (3 equiv.), K₂OsO₂(OH)₄ (1.0 mol%) and methanesulfonamide (1 equiv.) were dissolved in anhydrous CH₂Cl₂ (20 mL mmol⁻¹ substrate). In a Schlenk tube equipped with stirring bar and septum under a N₂ atmosphere, bispyridine)iodonium tetrafluoro-borate (1.1 equiv.) was dissolved in CH₂Cl₂ (20 mL mmol⁻¹ substrate). 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). 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.

(3R,4S)-4-Hydroxy-3-methylidihydrofuran-2(3H)-one (19): yield (0.25 mmol scale): 74%; 94% ee; colorless oil. 1H NMR: δ = 4.61 (d, 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 (CH), 17.40 (CH), 12.59 (CH); MS: m/z = 226 (M⁺, 14), 127 (1%, 19), 99 (M⁺–I, 32), 71 (C₃H₅O₂, 26), 55 (C₅H₇O, 100); HR-MS: m/z = 226.9562; calcd. for C₅H₇O₂: 226.9563; [α]D²⁰ = −16.9 [c 1.0, CHCl₃]. 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): 44.8 (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, (bispyridine)iodonium tetrafluoroborate (1.1 equiv.) was dissolved in CH₂Cl₂ (20 mL mmol⁻¹ substrate). The reaction mixture was cooled to −78°C and HBF₄ (55% 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.

(3R,4S)-4-Hydroxy-3-methylidihydrofuran-2(3H)-one (19): yield (0.25 mmol scale): 74%; 94% ee; colorless oil. 1H NMR: δ = 4.61 (d, 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 (CH), 17.40 (CH), 12.59 (CH); MS: m/z = 226 (M⁺, 14), 127 (1%, 19), 99 (M⁺–I, 32), 71 (C₃H₅O₂, 26), 55 (C₅H₇O, 100); HR-MS: m/z = 226.9562; calcd. for C₅H₇O₂: 226.9563; [α]D²⁰ = −16.9 [c 1.0, CHCl₃]. 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): 44.8 (R,S)-enantiomer, 45.0 (S,R)-enantiomer.
(35,4R)-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); 37.88 (CH3); MS: m/z = 226 (M+), 1, 127 (15), 15, 56 (C3H8O, 13), 55 (C7H14O, 100); HR-MS: m/z = 226.9563, calcd. for C12H23O2: 226.9563; [α]D = +19.2 [c 1.0, CH2Cl2], sample contains traces of (3R, 4S)-4-iodo-3-methylhydrofururan-2(3H)-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)-enantimeter, 44.6 (S,R)-enantimeter, 44.8 (R,S)- enantimeter of 5-membered lactone.

(S,E)-2-Methyldecal-3-enoic acid (21): prepared via the general procedure for the dehydration 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 (d, 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 (CH), 31.82 (CH), 29.24 (CH), 28.94 (CH2), 22.76 (CH), 17.43 (CH3), 14.23 (CH); MS: m/z = 184 (M+), 74 (72), 69 (C7H8O, 55 (C3H7O, 100); HR-MS: m/z = 185.1533, calcd. for C11H12O2: 185.1536; [α]D = +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 HBPin (54% in Et2O, 1.5 equiv.) was added whereupon the solution turned pink. Then the substrate dissolved in CH2Cl2 (20 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 with 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.

(3R,4S,5R)-5-Hexyl-4-iodo-3-methylhydrofururan-2(3H)-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 = 174.52 (C), 85.93 (CH), 47.02 (CH), 32.17 (CH), 31.67 (CH), 29.00 (CH), 25.49 (CH2), 25.13 (CH2), 22.65 (CH), 16.49 (CH3), 12.50 (CH3); MS: m/z = 225 (M+–hexyl, 3), 109 (C7H14O, 32), 109 (C7H14O, 33), 83 (C7H8O, 58), 69 (C6H12O, 57), 55 (C5H10O), 100; HR-MS: m/z = 225.9563, calcd. for C11H12O2: 225.9563; [α]D = +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[35] 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.

Acknowledgements

We thank T. D. Tiemersma-Wegman (GC, HPLC and MS) and A. Kiewiet (MS) for technical support (Stratingh Institute, University of Groningen). Financial support from the Netherlands Organization for Scientific Research (NWO) is gratefully acknowledged.

References


Copper-Catalyzed Asymmetric Allylic Alkylation of Halocrotonates:


[8] A Beilstein Crossfire search (January 6th 2010) identified 1563 natural products for α-Me-butyric acid with either a single or double bond and free sites at both the 4-position and the carboxylic acid moiety.


[10] This substrate was chosen mainly due to its physical properties (i.e., UV activity and low volatility).


[12] This kind of transformation has been observed more frequently, for example: in: J. J. Eisch, J. E. Gale, J. Org. Chem. 1979, 44, 3278–3279 (up to 76% yield) and in ref.[74] (up to 28% yield).

[13] The formation of the cyclopropane product 8b can be optimized and will be reported in due course.

[14] Benzyl crotonate is formed via Br-Mg exchange and subsequent quenching during work-up. Studies on this reagent will be disclosed shortly.

[15] The reaction has been performed at 10 mmol scale as well and gave 88% yield and 96% ee. By improving the experimental conditions (presumably longer addition of the substrate to the reaction mixture is required) higher ee might be obtained.

[16] Apparently allowing the reaction to proceed for 40 h gives slightly lower yield. The slightly lower ee might be explained by analysis issues due to overlapping of the large first peak and small second peak for this enantiomer on the chiral HPLC.


[20] The reduced carboxylic acid has also been obtained by asymmetric hydrogenation in excellent ee: a) ref.[107]; b) ref.[109]


[23] With respect to the higher ee measured for the iodolactonization products (vide infra) there might be a small impurity under the minor peak on the chiral GC and the ee might be higher.


[26] Storage of 12 for extended time at ~20°C (checked after 7 days) also gives lactonization.


[36] The observed enantioselectivities in this reaction are representative for terminal olefins.


[39] According to the literature, the 5-membered lactone products possess the all-trans configuration: J.-M. Garnier, S. Robin, R. Guillot, G. Rousseau, Tetrahedron: Asymmetry 2007, 18, 1434–1442. In NOESY-NMR experiments for 19 [(3R,4S)-3-iodo-3-methylidihydrofuran-2(3H)-one] we found a stronger coupling between one of C5 protons and the C4 proton and a weaker coupling with the other C5 proton and the C4 proton. The weaker coupling is as strong as the coupling of the protons of C4 and C3. For 22 [(3R,4S,SR)-5-ethyl-4-iodo-3-methylidihydrofuran-2(3H)-one] we found a weak coupling between the protons of C5 and C4 and a coupling similar in strength for the C4 and C3 protons. In combination with the expected trans-conformation for the protons of C4 and C3 arising from anti-addition of the carboxylate on the iodonium intermediate this most likely indicates an all-trans conformation of both 19 and 22.


[42] At higher concentration using the same reagents, the 5-membered lactone was obtained in low yield. This product is presumably formed by iodination of the olefin followed by S2 attack of the carboxylate on the terminal iodolakane.


[45] Using 21 (1 equiv.), I2 (5 equiv.), K2PO4 (5 equiv.), CH3Cl (9.5 mL in 21), room temperature, 16 h, the 5-membered product 22 was obtained in 77% yield. However, this yield was calculated from an impure spectrum containing an inseparable C3-phthalate from the CH3Cl used for the work-up of this reaction.


[54] Occasionally the product was polluted with 2,6-dichlorobenzoquinone, in these cases a yellow oil was obtained.


