Enantioselective copper catalyzed allylic alkylation using Grignard reagents; Applications in synthesis
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Chapter 4
Catalytic enantioselective synthesis of vicinal dialkyl arrays

In this chapter a new protocol for the synthesis of chiral vicinal dialkyl arrays is described. Using consecutive copper catalyzed enantioselective allylic alkylation, ruthenium catalyzed metathesis and asymmetric copper catalyzed conjugate addition reactions it is possible to synthesize compounds containing a vicinal dialkyl motif. In this fashion, almost complete catalyst stereocontrol, which overrules the inherent substrate control, is achieved. This allows the synthesis of either stereoisomer with excellent stereoselectivity. The versatility of this protocol in natural product synthesis is demonstrated in the preparation of the ant pheromones lasiol and faranal.*

* This chapter has been published in part: van Zijl, A. W.; Szymanski, W.; López, F.; Minnaard, A. J.; Feringa, B. L. J. Org. Chem. 2008, 73, 6994-7002.
4.1 Introduction

In the synthesis of chiral natural products with multiple stereogenic centers, it is imperative that the stereochemistry of each of these centers can be controlled. Therefore, methods that allow for the introduction of each stereochemical element independently (reagent or catalyst control), as opposed to being dependent on chirality introduced previously (substrate control), are an invaluable addition to the synthetic chemist’s tool-box. The Cu-catalyzed asymmetric allylic alkylation (AAA) and conjugate addition (CA) are two powerful C-C bond forming reactions enabling the formation of stereogenic centers with alkyl substituents. As discussed in chapter 2, we have recently reported catalysts based on copper and diphosphine ligands (Figure 4.1), that can perform both the enantioselective Cu-catalyzed allylic alkylation and conjugate addition using Grignard reagents. These reactions provide the chiral products in high yields and with excellent regioselectivity and enantiomeric excess.

Figure 4.1: Diphosphine ligands for asymmetric Cu-catalyzed conjugate addition and allylic alkylation with Grignard reagents.

Iterative protocols based on the enantioselective Cu-catalyzed conjugate addition for the synthesis of compounds with two or more stereocentres in a 1,3-relation or 1,5-relation to each other have been developed in our group, recently (see section 4.1.3). The utility of these protocols has been demonstrated in the total synthesis of several natural products. However, these approaches do not provide for the stereoselective synthesis of vicinal (1,2-relation) dialkyl arrays.
This chapter will discuss the development of a versatile protocol for the synthesis of such vicinal 1,2-dialkyl arrays based on three successive modern catalytic transformations (Scheme 4.1). The strategy consists of initial Cu-catalyzed asymmetric allylic alkylation (AAA) to build the first stereogenic center, a subsequent cross-metathesis (CM) reaction,\textsuperscript{11} which transforms the terminal alkene moiety generated into an $\alpha,\beta$-unsaturated system, and finally a Cu-catalyzed enantioselective conjugate addition (CA) of a Grignard reagent, which delivers the desired 1,2-dialkyl motif. In this manner, adjacent stereocentres with simple alkyl substituents are introduced with independent control of the stereochemistry, \textit{i.e.} both diastereomers, \textit{syn} and \textit{anti}, can be prepared selectively. Furthermore, this protocol was applied in the synthesis of the two ant pheromones lasiol and faranal.

\begin{center}
Scheme 4.1: Synthetic protocol providing vicinal dialkyl compounds (LG = leaving group).
\end{center}

\subsection*{4.1.1 The presence of vicinal dialkyl arrays in natural products}

The vicinal dialkyl motif is not as frequently encountered as, for instance, the ubiquitous 1,3-dimethyl deoxypropionate unit in polyketide derived natural products. Nevertheless, dialkyl arrays and in particular the 1,2-dimethyl motif can be found in a wide variety of compounds from many different natural product classes (Figure 4.2 and Schemes 4.2-4.4).

The motif is common in lignans, neolignans and other related compounds (\textit{e.g.} compounds 2 and 4, Figure 4.2).\textsuperscript{12} These natural products, which can be isolated from vascular plants, are phenylpropanoid dimers, \textit{i.e.} they are biosynthesized from two cinnamic acid residues. Many plant extracts used in traditional medicine contain mixtures of several lignans and these compounds have a number of medically important biological functions and effects. This makes them important lead structures for drug development.\textsuperscript{13}
1,2-Dimethyl arrays are present in the side chains of several steroid compounds. They are particularly common in withanolides, which contain dimethyl substituted lactones in the side chain. The biologically active withanolides can be isolated from several plant species from the Solanaceae family also known as the nightshade or the potato family. Many steroid compounds isolated from marine organisms, including starfish metabolite 1 (Figure 4.2), feature the 1,2-dimethyl motif in their side chains, also.

The marine neurotoxin kalkitoxin (5) (Figure 4.2), a secondary metabolite from the cyanobacterium Lyngbya majuscula, bears the vicinal dimethyl array. The dinoflagellate Gambierdiscus toxicus, implicated in ciguatera food poisoning, produces several polycyclic ether neurotoxins: both ciguatoxin (Scheme 4.2) and maitotoxin contain a dimethyl motif, either as part of one of the cyclic ethers (ciguatoxin) or in a side chain of the final ring (maitotoxin).
Finally, some insects produce pheromones containing the motif, e.g. faranal (3) and lasiol (vide infra). The stereochemical nature and purity of pheromones can be highly relevant to their bioactivity.\(^\text{19}\) As is obvious from the examples given, a synthetic method allowing for the preparation of either enantiomer of both the syn and the anti-motif (both present in these compounds, see Figure 4.2) of vicinal dialkyl, and in particular dimethyl arrays, would be invaluable.

### 4.1.2 Methods previously reported for the asymmetric synthesis of vicinal dialkyl arrays

#### 4.1.2.1 Stoichiometric methods

Most of the existing methods for the asymmetric synthesis of vicinal dialkyl arrays are based on chiral pool or chiral auxiliaries and reagents. For instance, a substrate controlled stereospecific Ireland-Claisen rearrangement was applied to construct the vicinal dimethyl containing L ring of ciguatoxin (6) (Scheme 4.2).\(^\text{20}\)

![Scheme 4.2: Ireland-Claisen rearrangement applied in the total synthesis of ciguatoxin (6); i) LDA, TMSCI, HMPA, THF, \(-78\ ^\circ\text{C} \rightarrow \text{rt}, 82\ \%\), dr = 3 : 1; dr = diastereomeric ratio; TIPDS = -Si(i-Pr)\(_2\)OSi(i-Pr)\(_2\).](image)

Chiral auxiliary based conjugate additions with MeMgBr and CuBr-SMe\(_2\) were used in the introduction of the second methyl group of the side chain of maitotoxin\(^\text{21}\) and in the total synthesis of kalkitoxin.\(^\text{16}\) In both cases the other methyl group had been introduced earlier in the synthesis. Both methyl groups can be introduced through a 1,4-addition and subsequent \(\alpha\)-alkylation also. Hanessian and coworkers used this approach in the synthesis of manassantins (a class of dineolignans). Their approach relied upon diastereoselective substrate control induced by the stereogenic
center at the γ-position (Scheme 4.3). The groups of Badía and White performed these reactions in one pot, i.e. 1,4-addition / enolate trapping, using chiral auxiliaries.

Scheme 4.3: Substrate control in 1,4-addition and subsequent α-alkylation in the synthesis of manassantin B (7); i) Me₂CuLi, TMSCl, THF, 87%, dr = 12 : 1; ii) KHMS, MeI, THF, 85%, dr = 12 : 1.

Scheme 4.4: Reagent controlled tiglylation followed by diastereoselective hydroboration in the synthesis of interiotherin A (8); i) CH₂Cl₂, -50 °C → 0 °C, 78%, dr = 100 : 0, 96% ee; ii) TBSCI, 2,6-lutidine; iii) 9-BBN, THF, 0 °C; iv) ArBr, Pd(PPh₃)₄, Ph₃P, NaOH, THF, 70 °C, 77%.

Reagent controlled introduction of the first methyl group by asymmetric tiglylation was applied in the syntheses of several dibenzocyclooctadiene lignan natural products. Tiglylating reagents based on several metals (e.g. B, Cr, Sn, In, and Si) were explored. Reaction with a chiral tiglylsilicon
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reagent proved to be the most selective (Scheme 4.4). Subsequent hydroboration of the gem-disubstituted double bond of the product yielded the vicinal dimethyl motif.

Michael reactions with the appropriate enolate nucleophile can provide vicinal dialkyl arrays, also. This has been applied in the syntheses of 3,4-dimethylglutamine (chiral auxiliary) and roccellic acid (chiral suloxide electrophile).25

4.1.2.2 Catalytic methods

As discussed in chapter 1, the replacement of stoichiometric methods for the synthesis of chiral compounds with catalytic protocols is highly desirable. The copper catalyzed Mukaiyama-Michael reaction, developed by the group of Evans, allows for the catalytic enantioselective synthesis of an anti vicinal dimethyl array in high enantioselectivity and diastereoselectivity (88%, 99 : 1 dr, 98% ee).26 Using their chiral oxazaborolidinone catalyst, Harada and coworkers reported the formation of a syn-diastereomer through use of an enolsilane with opposite double bond geometry, albeit with lower selectivity (54%, 8.8 : 1 dr, 75% ee).27

Catalytic desymmetrization of vicinal dimethyl containing meso-compounds is another efficient method to obtain these target structures. For instance, the desymmetrization of cyclic anhydrides provides for anti-dialkyl bearing compounds with differentiated carbonyl functionalities: e.g. hemiesters28 or keto acids29. The Rh-catalyzed coupling to diarylzinc reagents was used in the total synthesis of three different eupomatilones.29a

Scheme 4.5: Base catalyzed desymmetrization of a cyclic epoxide; i) 5 mol% catalyst, LDA, DBU, THF, 0 °C, 95%, 9 : 1 dr, 94% ee (major).

Another elegant example is the base catalyzed desymmetrization of cyclic epoxides to allylic alcohols (Scheme 4.5).30 A major disadvantage is
that the diastereomers of the substrate could not be separated from each other, inherently providing the product in the same ratio of diastereomers. In all of the desymmetrization reactions on cyclic compounds only the \textit{anti}-dialkyl diastereomer can be obtained.

4.1.3 Catalytic asymmetric protocols that provide independent control of arrays of chiral centers

The existing methods, described in section 4.1.2 are all either non-catalyzed or the two chiral centers cannot be controlled independently (\textit{vide supra}). Independent control of the stereochemistry of each stereochemical element enables one to prepare all possible diastereomers of a compound. This can be an advantage if, for instance, the complete stereochemical configuration of a natural product is not yet known. Some examples of this approach have been reported in the literature for 1,3- and 1,5-dimethyl motifs.

![Scheme 4.6: Enantioselective copper catalyzed conjugate addition of zinc reagents to cyclooctadienone to obtain the different diastereomers of 1,5-dimethyl building blocks; β-mannosyl phosphomycoketide (9); i) 5 mol% Cu(OTf)$_2$, 10 mol% L*, Me$_2$Zn, PhMe, $-25 \, ^\circ\mathrm{C}$, 85%, $>99\%$ ee; ii) 2.5 mol% Cu(OTf)$_2$, 5 mol% L*, Me$_2$Zn, CH$_2$Cl$_2$, $-25 \, ^\circ\mathrm{C}$ then Et$_3$N, TMEDA, TMSOTf, Et$_2$Zn, rt, $>98\%$ de; iii) 2.5 mol% Cu(OTf)$_2$, 5 mol% \textit{ent}-L*, Me$_2$Zn, CH$_2$Cl$_2$, $-25 \, ^\circ\mathrm{C}$ then Et$_3$N, HMPA, TMSCl, Et$_2$Zn, rt, $>98\%$ de; iv) 1. O$_3$, MeOH, CH$_2$Cl$_2$, $-78 \, ^\circ\mathrm{C}$ then NaBH$_4$, rt, 2. MeOH, TMSCl, reflux, 45% in two steps.](image-url)
The consecutive conjugate addition of dimethyl zinc to cyclooctadienone can be used to obtain any of the four possible stereoisomers of an acyclic chiral isoprenoid building block (1,5-dimethyl) depending on the ligand used in the reactions (Scheme 4.6). This reaction has been applied in the synthesis of two apple leafminer pheromones\textsuperscript{9} and β-mannosyl phosphomycoketide (9),\textsuperscript{10d} a mycobacterial antigen isolated from \textit{Mycobacterium tuberculosis}. In principle, this protocol allows for the synthesis of all possible stereoisomers of the alkyl chain.

Deoxypropionate units (1,3-dimethyl) are a common motif in natural products, also. Several ways exist to prepare the different diastereomers with high stereoselectivity through substrate or reagent control.\textsuperscript{31} Efficient catalytic methods that allow independent stereocontrol over each stereogenic center have, only recently, begun to appear. For instance, the copper catalyzed conjugate addition of Me\textsubscript{2}Zn to unsaturated malonate esters could be performed with high enantioselectivity.\textsuperscript{8b} The product could be extended in four steps to provide a new unsaturated malonate substrate for the conjugate addition. Both diastereomers of the product of the second 1,4-addition could be obtained in high diastereomeric ratio depending on the enantiomer of the ligand used.

Recently, Negishi and coworkers developed a Zr-catalyzed asymmetric carboalumination of alkenes, the ZACA-reaction (Scheme 4.7).\textsuperscript{32} The stereoselectivity of the reaction (in general ca. 80-90\% ee) is not as high as in other state-of-the-art enantioselective transition metal catalyzed reactions. However, the amplification of the enantiomeric excess through multiple enantioselective reactions is elegantly utilised by separating the diastereomers of the product at a later stage.

In other cases, an enzymatic resolution of the enantiomerically enriched compounds provides optically pure products. The combination of the enantioselective reaction and the resolution is far more effective than either method on its own. This protocol has been applied in several natural product syntheses,\textsuperscript{32a,33} including both \textit{syn} and the less common \textit{anti} arrays, \textit{e.g.} compound 10 (Scheme 4.7), which was isolated from the cuticle of the cane beetle \textit{Antitrogus parvulus}.\textsuperscript{33a}

In principle, the iterative sequence needs a single step to introduce one methyl substituent, providing an extended terminal olefin in each reaction.
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(for example Scheme 4.7, reaction iii). However, an alcohol functionality is needed to separate the diastereomers or perform the enzymatic resolution. This prevents the continuous one-step introduction of the methyl substituents.

Scheme 4.7: Zr-catalyzed asymmetric carboalumination of alkenes (ZACA-reaction) applied in the synthesis of hydrocarbon 10; i) 1. Me₃Al, 4 mol% cat., CH₂Cl₂, rt then O₂, (81%, 6 : 1 dr before enzymatic purification), 2. Amano PS lipase, vinyl acetate, CH₂Cl₂, 60%, >95 : 5 dr; ii) 1. I₂, PPh₃, 2.) t-BuLi, Et₂O, −78 °C then ZnBr₂ then vinyl bromide, Pd(PPh₃)₄; iii) 1. Me₃Al, 3 mol% ent-cat., CH₂Cl₂, 2. evaporation of Me₃Al and CH₂Cl₂ then Zn(OTf)₂, DMF, 70 °C, 3. Pd(DPEphos)Cl₂, DIBAL-H, vinyl bromide, 70%; iv) Me₃Al, 4 mol% cat., CH₂Cl₂, rt then O₂, (80%, 4 : 1 dr before chromatographic purification), 45%, >98 : 2 dr.

The enantioselective copper catalyzed conjugate addition of Grignard reagents to α,β-unsaturated thioesters, discussed in chapter 2, allows for the iterative synthesis of deoxypropionate units, also. The reaction proceeds in excellent enantioselectivity and the resulting saturated thioester can be transformed readily in two steps to an extended α,β-unsaturated substrate for a consecutive 1,4-addition (Scheme 4.8). Both diastereomers of the product can be obtained in high diastereoselectivity depending on the enantiomer of the ligand used.

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Several natural product syntheses of compounds containing multiple syn deoxypropionate units have been performed using this protocol. Although more steps are needed per iterative methyl introduction than with the ZACA-reaction, the much higher stereoselectivity and yields provide for a higher overall yield. For instance, the pheromone lardolure (11) was obtained in 26% overall yield after 12 steps and the heptamethyl-branched phthioceranic acid (12) was prepared in 24 steps with a 4% overall yield.

A similar approach, which makes use of 1,4-addition to oxoesters, was reported recently. The use of oxoesters allows the two steps, needed to transform the conjugate addition product into an extended substrate, to be performed in one pot.
4.1.4 Application of cross-metathesis to allylic alkylation products

The approaches to the preparation of 1,5- and 1,3-dimethyl arrays, discussed in section 4.1.3, allow independent stereocontrol of the created stereocenters. The intended catalytic protocol, discussed at the beginning of section 4.1 (Scheme 4.1), should enable the asymmetric synthesis of vicinal dialkyl arrays with similar independent stereocontrol of the adjacent stereogenic centers. The catalytic sequence will utilize a cross-metathesis reaction to transform the product of an enantioselective copper catalyzed allylic alkylation into a substrate for enantioselective 1,4-addition.

There are precedents for the use of cross-metathesis to further functionalize the products of Cu-catalyzed asymmetric allylic alkylation. For example cross-metathesis reactions with methyl vinyl ketone or acrylates, providing γ-chiral α,β-unsaturated carbonyl compounds, have been reported.35

Scheme 4.9: Total synthesis of elenic acid through copper catalyzed asymmetric allylic alkylation and cross-metathesis; i) 35 mol% HG-2, THF, 40 °C, 40 %, 3 : 1 E/Z; ii) BBr3, CH2Cl2, −78 °C → rt, 85%.

Hoveyda and coworkers applied cross-metathesis to the total synthesis of elenic acid.36 The natural product was obtained in only two steps after the allylic alkylation (Scheme 4.9); however, the cross-metathesis partner had to be synthesized in six steps. As a significant decrease in the enantiomeric
excess was not observed, the utility of the combination of these two reaction in total synthesis was demonstrated clearly, although the catalyst loading (35 mol%) and $E/Z$ ratio (3:1) leave room for improvement.

The transformation via cross-metathesis of a product of asymmetric allylic alkylation to another substrate for allylic alkylation was reported by the group of Hoveyda, also (Scheme 4.10).37 The product could be converted to a new substrate in three steps. Asymmetric allylic alkylation of this substrate with dimethylzinc provided the anti-product, containing a vicinal dialkyl motif, efficiently. However, the substrate was almost unreactive to allylic alkylation with the enantiomer of the ligand. Although this implies that the racemic substrate might be eligible for kinetic resolution using this reaction, ideally it would be possible to prepare both diastereomers in high selectivity. The proposed protocol of enantioselective copper catalyzed allylic alkylation, cross-metathesis and asymmetric copper catalyzed 1,4-addition (Scheme 4.1, *vide supra*) should provide access to all stereoisomers of these relevant vicinal dialkyl synthons.

Scheme 4.10: Allylic alkylation of a chiral substrate obtained through Cu-AAA and cross-metathesis; i) 1. *cis*-1,4-diacetoxybut-2-ene, 10 mol% H*G*-2, CH$_2$Cl$_2$, rt, 2. K$_2$CO$_3$, MeOH, 3. CIPO(OEt)$_2$, DMAP, Et$_3$N, 44% in three steps; ii) 5 mol% (CuOTf)$_2.C_6$H$_5$, 10 mol% L*, Me$_2$Zn, THF, −15 °C, 91%, >98% de; iii) 5 mol% (CuOTf)$_2.C_6$H$_5$, 10 mol% *ent*-L*, Me$_2$Zn, THF, −15 °C, 10-15% conv., <5% de.
4.2 Results and Discussion

4.2.1 Synthesis of chiral substrates for conjugate addition through allylic alkylation and metathesis

The Cu-catalyzed allylic alkylations were performed as discussed in chapter 2, with cinnamyl bromide 13 as a model substrate and MeMgBr or EtMgBr as Grignard reagents. The reactions were performed in CH$_2$Cl$_2$ at $-75^\circ$C in the presence of a copper catalyst, which was preformed in situ from CuBr·SMe$_2$ and ligand L$_2$, Taniaphos (Figure 4.1, vide supra). The enantioselective allylic alkylation is high yielding and gives the chiral product with excellent enantioselectivity (Table 4.1). In the AAA with methylmagnesium bromide the regioselectivity is high (>97 : 3). However, the AAA with ethyl magnesium bromide provided a mixture of SN$_2$' and SN$_2$ products 14 and 15 in a ratio of 80 : 20. Since 14 and 15 were inseparable by standard column chromatography, the cross-metathesis reactions were performed on the mixture. Consequently, for R = Et the cross-metathesis reaction leads to both products 17 and 18 from 14 and 15, respectively (Scheme 4.11).

Scheme 4.11: Formation of distinct products in copper catalyzed asymmetric allylic alkylation (AAA) and subsequent cross-metathesis (CM).
Catalytic enantioselective synthesis of vicinal dialkyl arrays

Our previous reports on the enantioselective Cu-catalyzed conjugate addition have focused on three types of acyclic substrates: α,β-unsaturated esters, ketones and thioesters. Therefore, three different electron deficient olefins 16 (Scheme 4.11) were used in the cross-metathesis reactions: methyl acrylate 16a, methyl vinyl ketone 16b and S-ethyl thioacrylate 16c. The results of the two-step syntheses of 17a-e are summarized in Table 4.1.

Table 4.1: Synthesis of 17a-e through allylic alkylation followed by cross-metathesis.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>16</th>
<th>(Figure 4.3)</th>
<th>17</th>
<th>yield(^b)</th>
<th>(ee(^c))</th>
<th>17 : 18(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>16a</td>
<td>(Y = OMe)</td>
<td>HG-2</td>
<td>17a</td>
<td>66%</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>16b</td>
<td>(Y = Me)</td>
<td>HG-2</td>
<td>17b</td>
<td>80% (99%)</td>
<td>&gt;97 : 3</td>
</tr>
<tr>
<td>3(^e)</td>
<td>Me</td>
<td>16c</td>
<td>(Y = SEt)</td>
<td>HG-2</td>
<td>17c</td>
<td>74% (97%)</td>
<td>&gt;97 : 3</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>16a</td>
<td>(Y = OMe)</td>
<td>HG-2</td>
<td>17d</td>
<td>67%(^g) (98%)</td>
<td>80 : 20</td>
</tr>
<tr>
<td>5(^f)</td>
<td>Et</td>
<td>16a</td>
<td>(Y = OMe)</td>
<td>G-2</td>
<td>17d</td>
<td>49%(^g) (98%)</td>
<td>90 : 10</td>
</tr>
<tr>
<td>6(^e)</td>
<td>Et</td>
<td>16c</td>
<td>(Y = SEt)</td>
<td>HG-2</td>
<td>17e</td>
<td>67%(^g) (97%)</td>
<td>80 : 20</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 1. 13 (1.0 equiv), CuBr·SMe\(_2\) (1.0 mol%), (+)-(R,R\(_F\))-L\(_2\) (1.2 mol%), RMgBr (1.2 equiv), CH\(_2\)Cl\(_2\), −75 °C; 2. 14 + 15 (1.0 equiv), 16 (5 equiv), Ru-cat (2 mol%), CH\(_2\)Cl\(_2\), rt; \(^b\) Isolated yield of 17 after two steps; \(^c\) Determined by chiral HPLC; \(^d\) Determined by \(^1\)H-NMR spectroscopy; \(^e\) 2 equiv of 16 used, 10 mol% catalyst added in two portions of 5.0 mol%; \(^f\) 1.5 mol% catalyst used; \(^g\) Calculated yield of 17 from 13 after two steps, based on overall yield and ratio of 17 and 18.

Compounds 17a and 17b, an α,β-unsaturated ester and ketone, respectively, with R = Me, could be obtained readily (Table 4.1, entries 1
and 2). The reactions were performed in CH₂Cl₂ at room temperature using five equivalents of olefin 16 and 2 mol% of the Hoveyda-Grubbs 2nd generation catalyst (HG-2, Figure 4.3). Compound 17c was obtained by a similar route using two equivalents of 16c and two portions of 5 mol% catalyst (Table 4.1, entry 3).

Despite the different reactivities of terminal and internal olefins, under the aforementioned conditions the S_N2-product 15 was transformed into the cinnamic acid derivative 18 quantitatively. This gave, in the case of 17d and 17e, where R = Et, a mixture of 17 and 18 (80 : 20), which was not separable (Table 4.1, entries 4 and 6). The reaction with the Grubbs 2nd generation catalyst (G-2, Figure 4.3) was more selective (90 : 10); however, this decreased the total yield of 17 (Table 4.1, entry 5).

4.2.2 Asymmetric conjugate addition reactions with Grignard reagents on the chiral metathesis products

4.2.2.1 Conjugate addition to chiral α,β-unsaturated esters

The results of the subsequent asymmetric 1,4-addition reactions with EtMgBr on the α,β-unsaturated esters 17a and 17d are summarized in Table 4.2. Stereoselective synthesis of a 1,2-methyl,ethyl motif was accomplished readily. Thus, depending on the enantiomer of ligand L3 used, either anti-19a or syn-19a was obtained in good yield and diastereoselectivity from substrate 17a (Table 4.2, entries 1 and 2). The synthesis of anti-19b, which has a diethyl motif, proceeded in good yield and diastereoselectivity from
The reaction using the ligand (S,R)-L3 was slower, however, providing syn-19b in 30% yield albeit with excellent diastereoselectivity (Table 4.2, entry 4). Introduction of a methyl substituent at the β-position with methyl Grignard reagent was not possible with this catalyst system, due to the insufficient reactivity of oxo esters.\footnote{40}

### Table 4.2: Asymmetric conjugate additions with Grignard reagents to α,β-unsaturated esters 17a and 17d.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>17</th>
<th>ligand</th>
<th>yield\textsuperscript{b}</th>
<th>anti : syn\textsuperscript{c}</th>
<th>ee\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>17a</td>
<td>(R,S)-L3</td>
<td>81%</td>
<td>99 : 1</td>
<td>&gt;99.5%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>17a</td>
<td>(S,R)-L3</td>
<td>84%</td>
<td>4 : 96</td>
<td>&gt;99.5%</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>17d</td>
<td>(R,S)-L3</td>
<td>77%</td>
<td>91 : 9</td>
<td>&gt;99.5%</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>17d</td>
<td>(S,R)-L3</td>
<td>30%\textsuperscript{d}</td>
<td>4 : 96</td>
<td>99%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: 17 (1.0 equiv), CuBr·SMe\textsubscript{2} (5.0 mol%), L3 (6.0 mol%), EtMgBr (5.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}, −78 °C, 18 h; \textsuperscript{b} Isolated yield of the mixture of diastereomers; \textsuperscript{c} Determined by chiral GC or HPLC; \textsuperscript{d} Conv. = 50%.\textsuperscript{41}

#### 4.2.2.2 Conjugate addition to chiral α,β-unsaturated ketones

The results of the asymmetric 1,4-addition to the α,β-unsaturated ketone 17b are summarized in Table 4.3. Enones are more active Michael acceptors than esters, which allows for the introduction of a second methyl group through 1,4-addition with this catalyst system. Thus, stereoselective synthesis of a 1,2-dimethyl motif was accomplished through 1,4-addition with MeMgBr (Table 4.3, entries 1 and 2). The product anti-20a could be obtained in high yield and excellent diastereoselectivity and enantiomeric excess, in contrast to the syn-product 20a, which was obtained in lower
yield and with reduced diastereoselectivity. Interestingly, the enantiomeric excess of the syn-product 20a was found to be 66%, which implies that racemization of the substrate occurs under the reaction conditions. When the reaction was performed with EtMgBr the same trend was observed (Table 4.3, entries 3 and 4), although substantial racemization was not observed.42

Table 4.3: Asymmetric conjugate additions with Grignard reagents to α,β-unsaturated ketones 17b.

<table>
<thead>
<tr>
<th>entry</th>
<th>R’MgBr</th>
<th>ligand</th>
<th>yield</th>
<th>anti : syn</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>(R,S)-L1</td>
<td>73%</td>
<td>98 : 2</td>
<td>&gt; 99.5%</td>
</tr>
<tr>
<td>2</td>
<td>MeMgBr</td>
<td>(S,R)-L1</td>
<td>46%</td>
<td>14 : 86</td>
<td>66%</td>
</tr>
<tr>
<td>3</td>
<td>EtMgBr</td>
<td>(R,S)-L1</td>
<td>89%</td>
<td>92 : 8</td>
<td>&gt; 99.5%</td>
</tr>
<tr>
<td>4</td>
<td>EtMgBr</td>
<td>(S,R)-L1</td>
<td>64%</td>
<td>40 : 60</td>
<td>97%</td>
</tr>
</tbody>
</table>

**Note:** Reaction conditions: 17b (1.0 equiv), CuBr\_L1 (7.0 mol%), R’MgBr (1.3 equiv), t-BuOMe, −78 °C, 18 h; b Isolated yield of the mixture of diastereomers; c Determined by chiral GC or HPLC.

4.2.2.3 Conjugate addition to chiral α,β-unsaturated thioesters

Compounds containing an α,β-unsaturated thioester are more reactive electrophiles than their corresponding oxo esters. Nevertheless, their synthetic versatility is similar. In our group, two catalysts that perform the 1,4-addition on thioesters effectively and selectively: Cu / JosiPhos L1 and Cu / Tol-BINAP L4, were reported previously. The results of the 1,4-additions are summarized in Table 4.4. Conjugate addition with methyl Grignard to the methyl containing substrate 17c gave product 21a with a 1,2-dimethyl motif. The performance of Tol-BINAP L4 was better in all
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aspects using MeMgBr (Table 4.4, entries 1-4). Although the use of L1 provided \textit{anti-21a} in good yield and excellent stereoselectivity, L4 provided the compound in higher yield and equally excellent selectivity. The other diastereomer \textit{syn-21a} could be obtained in good yield and excellent stereoselectivity with ligand L4, whereas a catalyst system with ligand L1 was significantly less active and selective (Table 4.4, entry 4 vs entry 2).

Table 4.4: Asymmetric conjugate additions with Grignard reagents to \(\alpha,\beta\)-unsaturated thioesters 17c and 17e.\(^{a}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R'MgBr</th>
<th>ligand</th>
<th>yield(^b)</th>
<th>(\textit{anti} : \textit{syn})(^c)</th>
<th>ee(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>17c</td>
<td>MeMgBr ((R,S)) - L1</td>
<td>\textit{anti-21a}</td>
<td>59%</td>
<td>99 : 1</td>
</tr>
<tr>
<td>2(^d)</td>
<td>Me</td>
<td>17c</td>
<td>MeMgBr (S,R) - L1</td>
<td>\textit{syn-21a}</td>
<td>17%</td>
<td>61 : 39</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>17c</td>
<td>MeMgBr ((R)) - L4</td>
<td>\textit{anti-21a}</td>
<td>96%</td>
<td>99.5 : 0.5</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>17c</td>
<td>MeMgBr (S) - L4</td>
<td>\textit{syn-21a}</td>
<td>82%</td>
<td>5 : 95</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>17c</td>
<td>EtMgBr ((R)) - L4</td>
<td>\textit{anti-21b}</td>
<td>91%</td>
<td>98 : 2</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>17c</td>
<td>EtMgBr (S) - L4</td>
<td>\textit{syn-21b}</td>
<td>58%</td>
<td>64 : 36</td>
</tr>
<tr>
<td>7(^d)</td>
<td>Et</td>
<td>17e</td>
<td>MeMgBr ((R,S)) - L1</td>
<td>\textit{anti-21c}</td>
<td>67%</td>
<td>98 : 2</td>
</tr>
<tr>
<td>8(^d)</td>
<td>Et</td>
<td>17e</td>
<td>MeMgBr (S,R) - L1</td>
<td>\textit{syn-21c}</td>
<td>6%(^c)</td>
<td>45 : 55</td>
</tr>
<tr>
<td>9</td>
<td>Et</td>
<td>17e</td>
<td>MeMgBr ((R)) - L4</td>
<td>\textit{anti-21c}</td>
<td>&lt;5%(^c)</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td>Et</td>
<td>17e</td>
<td>MeMgBr (S) - L4</td>
<td>\textit{syn-21c}</td>
<td>71%</td>
<td>12 : 88</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 17 (1.0 equiv), CuBr·L1 (6.0 mol%) or CuI (3.0 mol%) and L4 (3.3 mol%), R'MgBr (3.0-4.0 equiv), t-BuOMe, −75 °C, 18 h; \(^b\) Isolated yield of the mixture of diastereomers; \(^c\) Determined by chiral GC or HPLC; \(^d\) Reaction time: 40 h.
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The anti-diastereomer of product 21b could be obtained with excellent selectivity using ligand L4 and EtMgBr. However, product syn-21b could not be obtained selectively by this route (Table 4.4, entries 5 and 6). Curiously, stereoselective synthesis of anti-21c, which contains a 1,2-ethyl,methyl motif, could be accomplished with ligand L1, while the use of L4 was necessary to obtain the other diastereomer syn-21c. Hence the two ligand systems are complementary in this case (Table 4.4, entries 7-10).

4.2.3 Total synthesis of the ant pheromones (−)-lasiol and (+)-faranal

As discussed in section 4.1.1, in natural products, the 1,2-dimethyl motif is the most common of the vicinal dialkyl arrays. It is present, for example, in the two ant pheromones lasiol (22) and faranal (3) (Scheme 4.12). Lasiol is a volatile compound which was isolated from the mandibular glands of male Lasius meridionalis ants. Shortly after its discovery and racemic synthesis by Lloyd et al., both enantiomers of the pheromone lasiol were synthesized by Kuwahara et al. from the chiral pool and by Mori and co-workers using a non-catalytic desymmetrization similar to that in Scheme 4.5, mediated by a chiral base. Since then, several total syntheses and formal syntheses have followed.

Scheme 4.12: Retrosynthetic analysis of the ant pheromones lasiol (22) and faranal (3) to a common intermediate 23.

Faranal is the trail pheromone of Monomorium pharaonis, the pharaoh’s ant, a common pest in households, food storage facilities and hospitals. The absolute configuration of natural faranal was established through biological tests with diastereomeric mixtures of faranal, where one of the
stereogenic centers was set using an enzymatic condensation. Some stereoselective, but racemic syntheses have been published. The first truly asymmetric total synthesis of natural (+)-faranal (3) involved the resolution of a racemate, and was followed by other routes that made use of the chiral pool, chiral bases or enzymatic desymmetrization.

Importantly, in both natural products the vicinal 1,2-dimethyl motif has an anti configuration. Retrosynthetic analysis (Scheme 4.12) shows that they can be derived from a common intermediate 23, which can be obtained in turn through the allylic alkylation / cross-metathesis / conjugate addition protocol.

\[
\text{Scheme 4.13: Synthesis of common intermediate 23 via Cu-catalyzed enantioselective allylic alkylation, cross-metathesis and asymmetric conjugate addition.}
\]

Allylic alkylation of compound 26 with \(\text{MeMgBr}\) using the preformed complex \(\text{CuBr}(R,R,R)-\text{L2}\) as the catalyst gave product 27 in excellent yield, regioselectivity and enantioselectivity (Scheme 4.13). Cross-metathesis with thioacrylate 16c gave \(\alpha,\beta\)-unsaturated thioester 28 in good yield together
with a small percentage of the dimer 29 (ratio = 94 : 6).\textsuperscript{54} Conjugate addition to 28 with MeMgBr and (R)-L4 as the ligand gave \textit{anti}-23 in good yield and excellent diastereoselectivity. The other diastereomer \textit{syn}-23 could be obtained in high diastereoselectivity by using ligand (S)-L4 instead. In both cases the opposite enantiomer of the major diastereomer could not be detected, which highlights the potential of this protocol in synthesis.

(−)-Lasiol (22), which has the (2S,3S) absolute configuration,\textsuperscript{55} was synthesized from the common intermediate \textit{anti}-23. The thioester was first reduced to aldehyde 30 using DIBAL-H (Scheme 4.14). A Wittig reaction with isopropyltriphenylphosphonium iodide was performed to obtain benzyl ether 31, followed by quantitative deprotection of the alcohol using a dissolving metal reduction. Thus, (−)-lasiol (22) was synthesized in six steps from 26 in an overall yield of 60%.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{Scheme 4.14: Synthesis of (−)-lasiol (22) from common intermediate compound \textit{anti}-23 through reduction, Wittig reaction and deprotection of the benzyl ether.}};
\end{tikzpicture}
\end{center}

The synthesis of (+)-faranal (3) from compound \textit{anti}-23 started with its reduction to aldehyde 30 (Scheme 4.14, \textit{vide supra}). The aldehyde was subsequently protected as its acetal with ethylene glycol to give dioxolane 32 (Scheme 4.15). The benzyl ether was cleaved through hydrogenolysis with Pd(OH)\textsubscript{2} to furnish alcohol 33,\textsuperscript{56} which was converted to the alkyl iodide 25 using iodine, triphenylphosphine and imidazole. Compound 25 was converted in situ to the corresponding alkyl zinc bromide with tBuLi and ZnBr\textsubscript{2} and used in a Negishi-coupling reaction\textsuperscript{57} with alkenyl iodide 24, a known compound which was synthesized according to the methods of Baker et al.\textsuperscript{48b} and Mori et al.,\textsuperscript{51b} and catalytic [Pd(dpdpf)Cl\textsubscript{2}] to obtain
faranal precursor 34. Hydrolysis of the acetal in THF and water under dilute conditions completed the synthesis of (+)-faranal (3) in nine steps and an overall yield of 25% from the achiral precursor 26.

Scheme 4.15: Synthesis of (+)-faranal (3) from precursor 30 via protection of the aldehyde, hydrogenolysis, iodination and a Negishi coupling to 24, followed by deprotection.
4.3 Conclusions

In summary, a new protocol for the stereoselective synthesis of vicinal dialkyl arrays is reported. The protocol, which combines enantioselective allylic alkylation, cross-metathesis and enantioselective 1,4-addition, allows for the preparation of both of the diastereomers in enantiopure form with judicious choice of the ligands in the copper catalyzed reactions. The anti-diastereomer of the products was formed more easily than the syn-product in most cases, but on many occasions it was possible to form either diastereomer in high diastereoselectivity and excellent enantioselectivity. This demonstrates the high catalyst control versus substrate control in the conjugate addition to these γ-chiral α,β-unsaturated carbonyl compounds.

The protocols utility was demonstrated through the total syntheses of the ant pheromones (−)-lasiol and (+)-faranal, in six and nine steps, respectively, from an achiral precursor. The products were obtained with excellent diastereomeric and enantiomeric purity and high overall yields. These approaches comprise the shortest, highest yielding and most selective catalytic asymmetric total syntheses of these pheromones reported to date and are very competitive with existing methods, that employ the chiral pool, chiral auxiliaries or other methods based on stoichiometric chiral reagents.
4.4 Experimental Part

General Remarks: For general remarks, see the experimental part of previous chapters. In addition, the following remarks should be taken into account:

Ligand L4 and metathesis catalysts G-2 and HG-2 were purchased from Aldrich and used as received. Methyl acrylate 16a and methyl vinyl ketone 16b, were purchased from Aldrich and distilled under reduced pressure prior to their use. Compounds 16c^{38} and 24^{48b,51b} were prepared according to literature procedures. Et_{2}O and THF were distilled from Na/benzophenone and CH_{2}Cl_{2}, t-BuOMe and DMF (under reduced pressure) were distilled from CaH_{2}. Other solvents and reagents were used as received. Allylic alkylations, metathesis reactions and conjugate additions were conducted under a nitrogen atmosphere using standard Schlenk techniques.

Diastereomeric mixtures of racemic products for GC and HPLC reference were obtained by conjugate addition on the racemic metathesis products with the corresponding Grignard reagent (1.3 equiv) at 0 °C in Et_{2}O in the presence of CuI (1.3 equiv). The products 17b, 22, 3, 28 and 35 have been described previously (see appropriate references in the following pages). For experimental procedures of copper catalyzed allylic alkylations see preceding chapters: 14a (R = Me), 14b (R = Et) in chapter 2 and 27 in chapter 3.

(--)(S,E)-methyl 4-phenylpent-2-enoate (17a):

In a Schlenk tube equipped with septum and stirring bar, CuBr·SMe_{2} (15.0 μmol, 3.08 mg) and ligand L2 (18.0 μmol, 12.4 mg) were dissolved in CH_{2}Cl_{2} (3.0 mL) and stirred under argon at room temperature for 10 min. The mixture was cooled to −75 °C and MeMgBr (3.0 M solution in Et_{2}O, 1.73 mmol, 0.575 mL) was added dropwise. Following this, cinnamyl bromide (296 mg, 1.50 mmol) was added dropwise over 15 min via a syringe pump. Once the addition was complete the resulting mixture was stirred at −75 °C for 4 h. The reaction was quenched by addition of MeOH (0.5 mL) and the mixture was allowed to reach rt. Aqueous NH_{4}Cl solution (1M, 2 mL) was added to the mixture.
The organic layer was separated, and the resulting aqueous layer was extracted with Et₂O (0.5 mL, 3x). The combined organic layers were dried and concentrated to a yellow oil, which was dissolved in CH₂Cl₂ (3 mL) in a dry Schlenk tube under argon. Methyl acrylate (645 mg, 7.5 mmol) and Hoveyda-Grubbs 2nd generation catalyst (18 mg, 0.03 mmol) were added sequentially producing a light green solution which was stirred for 36 h at rt. The mixture was then concentrated in vacuo to a dark brown oil. Purification of this residue by silica gel chromatography (SiO₂, 2 : 98 to 5 : 95 Et₂O/n-pentane) afforded 17a as a colorless oil [66% yield, [α]D = −20 (c 0.3, CHCl₃)]; ¹H-NMR δ 7.29-7.25 (m, 2H), 7.21-7.14 (m, 3H), 7.07 (dd, J = 15.7 and 6.7 Hz, 1H), 5.77 (dd, J = 15.7 and 1.5 Hz, 1H), 3.67 (s, 3H), 3.61-3.54 (m, 1H), 1.38 (d, J = 7.1 Hz, 3H); ¹³C-NMR δ 167.1, 152.9, 143.2, 128.6, 127.3, 126.7, 119.6, 51.4, 42.0, 20.1; MS (EI) m/z 190 (M⁺, 40), 159 (18), 131 (100), 91 (22), 51 (13); HRMS Calcd. for C₁₂H₁₄O₂ 190.0994, found 190.0995.

(−)-(S,E)-5-phenyl-hex-3-en-2-one (17b): A solution of terminal olefin 14a (0.50 mmol) in dry CH₂Cl₂ (2.0 ml) was stirred under a N₂-atmosphere at room temperature. Methylvinylketone 16b (2.5 mmol) was added via syringe in one portion, followed by Hoveyda-Grubbs 2nd generation catalyst (6.3 mg, 2 mol%). The mixture was stirred overnight. After completion of the reaction, the solvent was evaporated, and the crude mixture was subjected to flash chromatography (silica gel, n-pentane – n-pentane/ethyl acetate 99.5:0.5, v/v) affording product 17b. Reaction time: 20 h. [90% yield, >99.5% ee, [α]D = −20.6 (c 1.0, CHCl₃)]; Rₜ = 0.50 (n-pentane/EtOAc, 9:1, v/v); ¹H NMR (400 MHz, CDCl₃): δ 1.43 (d, J = 6.8 Hz, 3H), 2.24 (s, 3H), 3.62-3.65 (m, 1H), 6.07 (dd, J = 16.0 and 1.2 Hz, 1H), 6.92 (dd, J = 16.0 and 6.8 Hz, 1H), 7.17-7.35 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 20.4, 27.2, 42.5, 127.1, 127.6, 129.0, 129.9, 143.5, 151.9, 199.2; MS (EI) m/z 174 (M⁺, 56), 131 (100), 91 (30); HRMS Calcd. for C₁₂H₁₄O 174.1045, found 174.1043; Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OB-H, n-heptane/i-PrOH, 98/2, v/v), retention times (min): 36.8 (R) and 40.9 (S).
(--)-Methyl (S,E)-4-phenyl-hex-2-enoate (17d):

The same procedure as 17b, although with olefins 14b and 16a, instead. Reaction time: 17 h. Reaction afforded a 80/20 mixture of 17d and 18. [95% yield, 98% ee, [α]D = −4.8 (c 0.27, CHCl3)]; Rf = 0.67 (n-pentane/EtOAc, 9:1, v/v); ¹H NMR (400 MHz, CDCl3): δ 0.88 (t, J = 7.2 Hz, 3H), 1.76-1.85 (m, 2H), 3.26-3.32 (m, 1H), 3.71 (s, 3H), 5.79 (dd, J = 16.0 and 1.2 Hz, 1H), 7.08 (dd, J = 16.0 and 8.0 Hz, 1H), 7.07-7.32 (m, 5H); ¹³C NMR (50 MHz, CDCl3): δ 12.0, 27.9, 50.2, 51.4, 120.4, 126.7, 127.7, 128.6, 142.1, 152.0, 167.0; MS (EI) m/z 204 (M+, 8), 145 (37), 115 (100); HRMS Calcd. for C13H16O2 204.1150, found 204.1162; Enantiomeric excess was determined by chiral HPLC analysis (Whelk, n-heptane/i-PrOH, 99.5:0.5, v/v), retention times (min): 20.1 (S) and 21.6 (R).

(--)-S-Ethyl (S,E)-4-phenyl-pent-2-enethioate (17c):

A solution of terminal olefin 14a (0.50 mmol) in dry CH₂Cl₂ (2.0 ml) was stirred under a N₂-atmosphere at room temperature. Ethyl thioacrylate (16c) (1.0 mmol, 116 μl) was added via syringe in one portion, followed by Hoveyda-Grubbs 2nd generation catalyst (5 mol%, 16.0 mg). After 8 h, another portion of Hoveyda-Grubbs 2nd generation catalyst (5 mol%, 16.0 mg) was added. Upon complete conversion of 14a (40 h), the solvent was evaporated, and the crude mixture was subjected to flash chromatography (silica gel, n-pentane – n-pentane/ethyl acetate 99.5:0.5, v/v) affording the product 17c. [83% yield, 97% ee, [α]D = −7.0 (c 1.0, CHCl3)]; Rf = 0.48 (n-pentane/Et₂O, 95:5, v/v); ¹H NMR (400 MHz, CDCl3): δ 1.27 (t, J = 7.2 Hz, 3H), 1.43 (d, J = 7.6 Hz, 3H), 2.93 (q, J = 7.2 Hz, 2H), 3.56-3.62 (m, 1H), 5.07 (dd, J = 15.6 and 1.6 Hz, 1H), 7.03 (dd, J = 15.6 and 6.8 Hz, 1H), 7.20-7.33 (m, 5H); ¹³C NMR (50 MHz, CDCl3): δ 14.8, 20.2, 23.1, 42.0, 126.8, 127.4, 128.7, 143.1, 148.4, 190.2; MS (EI) m/z 220 (M⁺, 24), 159 (100), 115 (37); HRMS Calcd. for C 13H16OS 220.0922, found 220.0921; Enantiomeric excess was determined by chiral HPLC analysis (Chiracel OD-H, n-heptane/i-PrOH, 99.5:0.5, v/v), retention times (min): 18.5 (S) and 21.2 (R).
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(−)-S-Ethyl (S)-4-phenyl-hex-2-enethioate (17e):

As for 17c, although with olefin 14b instead of 14a. Reaction time: 23 h. Reaction afforded a 80/20 mixture of 17e and 18. [95% yield, 97% ee, [α]D = −21.6 (~ 1.0, CHCl3);] Rf = 0.73 (n-pentane/EtOAc, 9:1, v/v); 1H NMR (300 MHz, CDCl3): δ 0.88 (t, J = 7.5 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.75-1.85 (m, 2H), 2.92 (q, J = 7.2 Hz, 2H), 3.22-3.30 (m, 1H), 6.05 (d, J = 15.3 Hz, 1H), 6.98 (dd, J = 15.3 and 8.1 Hz, 1H), 7.14-7.40 (m, 5H); 13C NMR (50 MHz, CDCl3): δ 12.1, 14.8, 23.1, 28.0, 50.2, 126.8, 127.8, 128.0, 128.7, 141.9, 147.5, 190.2; MS (EI) m/z 234 (M+, 25), 173 (100), 145 (46), 115 (32). HRMS Calcd. for C 14H18OS 234.1078, found 234.1087. Enantiomeric excess was determined by chiral HPLC analysis (Chiracel OJ-H, n-heptane/i-PrOH, 95:5, v/v), retention times (min): 10.5 (S) and 12.4 (R).

(+)-(3S,4S)-methyl 3-ethyl-4-phenylpentanoate (anti-19a):

In a Schlenk tube CuBr·SMe2 (8.0 μmol, 1.62 mg) and ligand (R,S)-L3 (9.4 μmol, 5.60 mg) were dissolved in CH2Cl2 (1.5 mL) and stirred under argon at room temperature for 10 min. The mixture was cooled to -75 °C and EtMgBr (3.0 M in Et2O, 0.78 mmol) was added dropwise. After stirring for 5 min at that temperature a solution of 17a (30 mg, 0.16 mmol) in CH2Cl2 (0.25 mL) was added dropwise over 10 min. After stirring at −75 °C for 22 h, MeOH (0.25 mL) and aq. NH4Cl (1M, 2 mL) were added sequentially, and the mixture was warmed to rt. After extraction with Et2O (0.5 mL, 3x), the combined organic layers were dried and concentrated to a yellow oil, which was purified by flash chromatography (SiO2, 2 : 99 Et2O/n-pentane) to yield anti-19a as a colourless oil [81% yield, 98% de, >99.5% ee (major diastereomer), [α]D = +25 (c 0.2, CHCl3)]; 1H-NMR δ 7.26-7.12 (m, 5H), 3.57 (s, 3H), 2.82-2.73 (m, 1H), 2.30-2.15 (m, 2H), 2.08-1.97 (m, 1H), 1.38-1.27 (m, 1H), 1.17 (d, J = 7.1 Hz, 3H), 1.14-1.06 (m, 1H), 0.81 (t, J = 7.4 Hz, 3H); 13C-NMR δ 174.1, 145.6, 128.2, 127.7, 126.0, 51.4, 42.8, 41.4, 35.3, 24.4, 17.1, 11.1; MS (EI) m/z 220 (M+, 20), 189 (11), 146 (43), 105 (100) 57 (21); HRMS Calcd. for C14H20O2 220.1463, found 220.1457. Diastereoselectivity was determined using a ChiralHPLC column (30 m x 0.25 mm), 100 °C
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Isothermic, retention times (min): 59.6 (minor: 3R,4S and 3S,4R) and 62.4 (major, 3S,4S). Alternatively, the diastereoselectivity was determined by 1H-NMR spectroscopy, by integration of the signals at 3.5 ppm corresponding to the methyl ester group. Enantiomeric excess was determined using a Chiraldex B-PM column (30m x 0.25mm), 85 °C isothermic, retention times (min): 240.5 (3S,4S), 245.5 (3R,4R).

(+)-(3R,4S)-methyl 3-ethyl-4-phenylpentanoate (syn-19a):

As for anti-19a however using (S,R)-L3 instead of (R,S)-L3. [84% yield, 92% de, >99.5% ee (major diastereomer), [α]D = +6 (c 0.6, CHCl₃)]; 1H-NMR δ 7.24-7.20 (m, 2H), 7.14-7.11 (m, 3H), 3.53 (s, 3H), 2.71-2.67 (m, 1H), 2.16-2.01 (m, 3H), 1.44-1.29 (m, 2H), 1.19 (d, J = 7.2 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H); 13C-NMR δ 174.0, 145.6, 128.2, 127.8, 126.1, 51.3, 42.5, 41.8, 36.3, 23.1, 18.2, 10.4; MS (EI) m/z 220 (M⁺, 18), 189 (12), 146 (58), 105 (100); HRMS Calcd. for C₁₄H₂₀O₂ 220.1463, found 220.1462. Diastereoselectivity was determined using a Chiraldex G-TA column (30 m x 0.25 mm), 100 °C, retention times (min): 59.6 (major: 3R,4S), 62.4 (minor: 3S,4S) and 63.3 (minor: 3R,4R). Alternatively, the de was determined by 1H-NMR spectroscopy, by integration of the signals at 3.57 and 3.53 ppm corresponding to the methyl ester groups. Enantiomeric excess was determined using a CP Chiralsil Dex CB column (25m x 0.25mm), initial T = 70 °C, gradient: 3 °C / min to 110 °C, 110 °C isothermic, retention times (min): 78.5 (3S,4R), 80.3 (3R,4S).

(+)-Methyl (3S,4S)-3-ethyl-4-phenylhexanoate (anti-19b):

The same procedure as for anti-19a however using 17d (contaminated with 18) instead of 17a afforded a mixture of syn-19b and anti-19b and the product of 18, which could be separated by column chromatography. [77% yield, 82% de, >99.5% ee (major diastereomer), [α]D = +9.4 (c 1.0, CHCl₃)]; Rf = 0.49 (n-pentane/Et₂O 95:5, v/v); 1H NMR (400 MHz, CDCl₃): δ 0.73 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.2 Hz, 3H), 0.98-1.08 (m, 1H), 1.35-1.45 (m, 1H), 1.59-1.76 (m, 2H), 2.06-2.10 (m, 1H), 2.28-2.31 (m, 2H), 2.47-2.53 (m, 1H), 3.67 (s, 3H), 7.12-7.30 (m, 5H); 13C NMR (50 MHz, CDCl₃): δ 11.1, 12.5, 23.8, 24.8, 35.9, 41.9, 50.2, 51.5, 126.0, 128.0, 128.7, 143.1, 174.2; MS (EI) m/z...
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234 (M+, 34), 160 (78), 119 (100), 91 (98); HRMS Calcd. for C_{15}H_{22}O_{2} 234.1620, found 234.1628. Diastereomeric ratio was determined by chiral GC analysis, CP Chiralsil Dex CB (25 m x 0.25 mm), initial temp. 75 °C, gradient: 3 °C/min; retention times (min): 29.8 (syn) and 30.0 (anti). Alternatively, the dr was determined by \(^1\)H NMR spectroscopy, by comparison of the \(\text{OCH}_3\) signals (3.66 ppm for anti, 3.58 ppm for syn). Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OJ-H, \(n\)-heptane/\(i\)-PrOH, 99/1, v/v, 40 °C), retention times (min): 11.1 (3R,4S) and 11.7 (3R,4R).

\((-\)-Methyl (3R,4S)-3-ethyl-4-phenylhexanoate (syn-19b):

The same procedure as for \(\text{anti-19a}\) however using \(17d\) (contaminated with \(18\)) instead of \(17a\) and \((S,R)-L3\) instead of \((R,S)-L3\) afforded a mixture of \(\text{syn-19b}\) and \(\text{anti-19b}\) and the product of \(18\), which could be separated by column chromatography. [30% yield, 92% de, 99% ee (major diastereomer), [\(\alpha\)]\(_D\) = +7.2 (c 0.5, CHCl\(_3\)); \(R_f = 0.49\) (\(n\)-pentane/\(Et_2O\) 95:5, v/v); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.72 (t, \(J = 7.2\) Hz, 3H), 0.90 (t, \(J = 7.2\) Hz, 3H), 1.38-1.45 (m, 2H), 1.53-1.62 (m, 1H), 1.76-1.82 (m, 1H), 2.01 (dd, \(J = 14.8\) and 8.4 Hz, 1H), 2.08-2.18 (m, 1H), 2.21 (dd, 1H, \(J = 14.8\) and 4.8 Hz), 2.45-2.53 (m, 1H), 3.58 (s, 3H), 7.11-7.31 (m, 5H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 10.4, 12.4, 23.8, 25.3, 36.2, 41.3, 49.7, 51.3, 126.1, 128.1, 128.7, 143.1, 174.2; MS (EI) \(m/z\) 234 (M\(^+\), 34), 160 (63), 119 (90), 91 (100). HRMS Calcd. for C_{15}H_{22}O_{2} 234.1620, found 234.1628. Diastereoisomeric ratio was determined by chiral GC analysis, CP Chiralsil Dex CB (25 m x 0.25 mm), initial temp. 75 °C, gradient: 3 °C/min; retention times (min): 29.8 (syn) and 30.0 (anti). Alternatively, the dr was determined by \(^1\)H NMR spectroscopy, by comparison of the \(\text{OCH}_3\) signals (3.66 ppm for anti, 3.58 ppm for syn). Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OJ-H, \(n\)-heptane/\(i\)-PrOH, 99/1, v/v, 40 °C), retention times (min): 11.7 (3R,4S) and 12.6 (3S,4R).

\((-\)-4(S,5S)-4-methyl-5-phenylhexan-2-one (anti-20a):

In a Schlenk tube, \((R,S)-L1\) (7.5 \(\mu\)mol, 5.54 mg) was dissolved in \(t\)-BuOMe (1.0 mL) and stirred under a \(N_2\)-atmosphere at room temperature for 10 min. The
mixture was cooled to −75 °C and MeMgBr (0.15 mmol, 3.0 M solution in Et₂O) was added dropwise. After stirring for 5 min at that temperature a solution of 17b (0.11 mmol, 20 mg) in dry t-BuOMe (0.5 ml) was added dropwise over 10 min. After 16 h, methanol (0.5 ml) was added and the mixture was allowed to reach rt. Aqueous NH₄Cl (2 ml) was added, and the biphasic system was stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with Et₂O (2 x 3 ml). The combined organic layers were dried (MgSO₄) and the solvent was evaporated. Flash chromatography (silica gel, n-pentane – n-pentane/Et₂O, 99.5:0.5, v/v) afforded a mixture of syn-20a and anti-20a. [73% yield, 96% de, >99.5% ee (major diastereomer), [α]₀ = +12.5 (c 1.0, CHCl₃); Rᵥ = 0.52 (n-pentane/EtOAc, 9:1, v/v). ¹H NMR (300 MHz, CDCl₃): δ 0.29 (d, J = 6.3 Hz, 3H) 1.27 (d, J = 6.9 Hz, 3H) 2.13 (s, 3H), 2.09-2.34 (m, 2H), 2.47-2.53 (m, 1H), 2.60-2.70 (m, 1H), 7.15-7.32 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 17.6, 18.1, 30.5, 35.2, 44.5, 48.2, 126.0, 127.9, 128.1, 145.1, 208.9; MS (EI) m/z 190 (M⁺, 8), 149 (35), 132 (100), 105 (86); HRMS Calcd. for C₁₃H₁₈O 190.1358, found 190.1352; Diastereoisomeric ratio and enantiomeric excess were determined by chiral GC analysis, CP Chiralsil Dex CB (25 m x 0.25 mm), initial temp. 75 °C, gradient: 3 °C/min; retention times (min): 26.4 (syn) and 25.8 (4S,5S), 26.1 (4R,5R). Alternatively, the dr was determined by ¹H NMR spectroscopy, by comparison of the COCH₃ signals (2.13 ppm for anti, 2.00 ppm for syn).

(+)-(4R,5S)-4-methyl-5-phenylhexan-2-one (syn-20a):

The same procedure as for anti-20a however using (S,R)-L1 instead of (R,S)-L1. Reaction time: 18 h. The reaction afforded a mixture of syn and anti isomers [46% yield, 72% de, 66% ee (major diastereomer), [α]₀ = +4.7 (c 0.3, CHCl₃, 84% ee, 92% de)⁵⁹]; Rᵥ = 0.58 (n-pentane/EtOAc, 9:1, v/v). ¹H NMR (300 MHz, CDCl₃): δ 0.94 (d, J = 6.3 Hz, 3H) 1.25 (d, J = 6.9 Hz, 3H) 2.00 (s, 3H), 2.09-2.34 (m, 3H), 2.45-2.58 (m, 1H), 7.15-7.32 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 17.4, 18.5, 30.4, 35.5, 45.1, 49.4, 126.1, 127.6, 128.3, 146.2, 209.0; MS (EI) m/z 190 (M⁺, 8), 149 (35), 132 (100), 105 (75); HRMS Calcd. for C₁₃H₁₈O 190.1358, found 190.1349; Diastereoisomeric ratio was determined by chiral GC analysis, CP Chiralsil Dex CB (25 m x 0.25 mm), initial temp. 75 °C, gradient: 3 °C/min; retention times (min): 26.4 (syn) and 25.8 (4S,5S), 26.1 (4R,5R). Alternatively, the dr
was determined by \(^1\)H NMR spectroscopy, by comparison of the COCH\(_3\) signals (2.13 ppm for \textit{anti}, 2.00 ppm for \textit{syn}). Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OJ-H, \textit{n}-heptane/\textit{i}-PrOH, 99/1, v/v, 40 °C), retention times (min): 20.8 (4S,5R) and 22.4 (4R,5S).

\textit{(+)-(4S,5S)-4-ethyl-5-phenylhexan-2-one (anti-20b):}

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\begin{align*}
\text{The same procedure as for anti-20a however using EtMgBr instead of MeMgBr. Reaction time: 16 h. The reaction afforded a mixture of \textit{syn} and \textit{anti} isomers [89% yield, 84% de, >99.5% ee (major diastereomer), } &[	ext{\(\alpha\)]\(_D\} = +8.4 \text{ (c 0.9, CHCl}_3]\}; \text{R}_f = 0.63 (\textit{n}-\text{pentane/\textit{EtOAc}, 9:1, v/v).} \text{\(^1\)H NMR (400 MHz, CDCl}_3): \text{\(\delta\) 0.85 (t, } J = 7.2 \text{ Hz, 3H), 1.18 (d, } J = 7.2 \text{ Hz, 3H), 1.10-1.40 (m, 2H), 2.06 (s, 3H), 2.13-2.18 (m, 1H), 2.26-2.39 (m, 2H), 2.82-2.86 (m, 1H), 7.17-7.31 (m, 5H); } \text{\(^{13}\)C NMR (50 MHz, CDCl}_3): \text{\(\delta\) 11.3, 16.7, 24.6, 30.2, 41.2, 41.5, 44.9, 126.0, 127.8, 128.1, 145.7, 209.0; MS (EI) m/z 204 (M\(^+\), 8), 146 (100), 131 (40), 105 (88)}; \text{HRMS Calcd. for C}_{14}\text{H}_{20}\text{O 204.1514, found 204.1519; Diastereoisomeric ratio was determined by chiral GC analysis, CP Chiralsil Dex CB (25 m x 0.25 mm), initial temp. 75 °C, gradient: 3 °C/min; retention times (min): 24.4 (\textit{syn}) and 25.3 (\textit{anti}). Alternatively, the dr was determined by \(^1\)H NMR spectroscopy, by comparison of the COCH\(_3\) signals (2.06 ppm for \textit{anti}, 1.96 ppm for \textit{syn}). Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H, \textit{n}-heptane/\textit{i}-PrOH, 99.5/0.5, v/v, 40°C), retention times (min): 15.3 (4S,5S) and 14.4 (4R,5R).}
\end{align*}
\]
Diastereoisomeric ratio was determined by chiral GC analysis, CP Chiralsil Dex CB (25 m x 0.25 mm), initial temp. 75 ºC, gradient: 3 ºC/min; retention times (min): 24.4 (syn) and 25.3 (anti). Alternatively, the dr was determined by ¹H NMR spectroscopy, by comparison of the COCH₃ signals (2.06 ppm for anti, 1.96 ppm for syn). Enantiomeric excess was determined on a derivative of syn-20b, the tertiary alcohol (4R,5S)-4-ethyl-2-methyl-5-phenylhexan-2-ol: To a cooled (0 ºC) solution of a sample of syn-20b in Et₂O was added MeMgBr (ca. 5 equiv), the reaction mixture was stirred at rt for 2 h, quenched with sat. aqueous NH₄Cl and extracted with Et₂O. GC analysis was performed on a crude sample of the tertiary alcohol: Chiraldex B-PM column (30m x 0.25mm), 85 ºC isothermic, retention times (min): 330.4 (4S,5R), 336.3 (4S,5S), 343.7 (4R,5R), 354.0 (3R,4S).

(+) -S-Ethyl (3S,4S)-3-methyl-4-phenylpentanethioate (anti-21a):

In a Schlenk tube Cul (3.3 µmol, 0.63 mg) and (R)-L₄ (3.6 µmol, 2.46 mg) were dissolved in CH₂Cl₂ (0.5 mL) and stirred under a N₂-atmosphere at room temperature for 50 min. The solvent was evaporated, and the residue was dissolved in t-BuOMe (1.2 ml). The mixture was cooled to −75 ºC and MeMgBr (3.0 M in Et₂O, 0.44 mmol) was added dropwise. After stirring for 5 min at that temperature a solution of 17c (0.11 mmol) in CH₂Cl₂ (0.4 mL) was added dropwise over 10 min. After stirring at −75 ºC for 18 h, MeOH (0.25 mL) and aq. NH₄Cl (1M, 2 mL) were added sequentially, and the mixture was warmed to rt. After extraction with Et₂O (0.5 mL, 3x), the combined organic layers were dried and concentrated to a yellow oil which was subjected to flash chromatography (silica gel, n-pentane/Et₂O 99.75:0.25, v/v) to afford syn-21a and anti-21a. [96% yield, 99% de, 99% ee (major diastereomer), [α]D = +31.4 (c 0.35, CHCl₃)]; Rf = 0.50 (pentane/Et₂O 95:5, v/v); ¹H NMR (400 MHz, CDCl₃): δ 0.80 (d, J = 6.8 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.27 (d, J = 6.4 Hz, 3H), 2.24-2.36 (m, 2H), 2.62-2.68 (m, 2H), 2.87 (q, J = 7.6 Hz, 2H), 7.15-7.31 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 14.8, 17.2, 18.5, 23.3, 37.0, 44.5, 48.8, 126.1, 127.8, 128.1, 144.8, 199.3; MS (EI) m/z 236 (M⁺, 12), 175 (100), 132 (35), 105 (66), 91 (30); HRMS Calcd. for C₁₄H₂₀O₂S 236.1235, found 236.1244. Diastereoisomeric ratio was determined by chiral GC analysis, Chiralsil GTA (25 m x 0.25 mm), initial temp. 75 ºC, gradient: 3 ºC/min; retention times (min): 30.0 (syn) and 30.6 (anti). Alternatively, the dr was determined.
by $^1$H NMR spectroscopy, by comparison of the PhCHCH$_3$ signals (doublet, 0.80 ppm for anti, 0.95 ppm for syn). Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H, $n$-heptane/i-PrOH, 99/1, v/v, 40°C), retention times (min): 12.3 (3S,4S) and 13.5 (3R,4R).

(+)-S-Ethyl (3R,4S)-3-methyl-4-phenylpentanethioate (syn-21a): The same procedure as for anti-21a however using (S)-L$_4$ instead of (R)-L$_4$. The reaction afforded a mixture of syn and anti isomers [82% yield, 90% de, >99.5% ee (major diastereomer), $\alpha_D = +23.0$ (c 1.0, CHCl$_3$)]; $R_f = 0.50$ ($n$-pentane/Et$_2$O 95:5, v/v); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.95 (d, $J = 6.8$ Hz, 3H), 1.21 (t, $J = 7.2$ Hz, 3H), 1.25 (d, $J = 6.4$ Hz, 3H), 2.16-2.33 (m, 2H), 2.44-2.62 (m, 2H), 2.83 (q, $J = 7.6$ Hz, 2H), 7.16-7.33 (m, 5H); $^{13}$C NMR (50 MHz, CDCl$_3$); $\delta$ 14.8, 16.6, 18.0, 23.2, 37.3, 44.7, 49.6, 126.2, 127.6, 128.3, 145.7, 199.4; MS (EI) $m/z$ 236 (M$^+$, 12), 175 (100), 132 (43), 105 (64), 91 (34); HRMS Calcd. for C$_{14}$H$_{20}$O$S$ 236.1235, found 236.1247. Diastereoisomeric ratio was determined by chiral GC analysis, Chiralsil G-TA (25 m x 0.25 mm), initial temp. 75 °C, gradient: 3 °C/min; retention times (min): 30.0 (syn) and 30.6 (anti). Alternatively, the dr was determined by $^1$H NMR spectroscopy, by comparison of the PhCHCH$_3$ signals (doublet, 0.80 ppm for anti, 0.95 ppm for syn). Enantiomeric excess was determined on a derivative of syn-21a, the tertiary alcohol (4R,5S)-2,4-dimethyl-5-phenylhexan-2-ol: To a cooled (0°C) solution of a sample of syn-21a in Et$_2$O was added MeMgBr (ca. 5 equiv), the reaction mixture was heated at reflux for 2 h, quenched with sat. aqueous NH$_4$Cl and extracted with Et$_2$O. GC analysis was performed on a crude sample of the tertiary alcohol: CP Chiralsil Dex CB column (25m x 0.25mm), initial T = 70 °C, gradient: 3 °C / min to 150 °C, 150 °C isothermic, retention times (min): 30.1 (4S,5R), 30.4 (4R,5S).

(+)-S-Ethyl (3S,4S)-3-ethyl-4-phenylpentanethioate (anti-21b): The same procedure as for anti-21a however using EtMgBr instead of MeMgBr. The reaction afforded a mixture of syn and anti isomers [91% yield, 96% de, 94% ee (major diastereomer), $\alpha_D = +13.0$ (c 1.0, CHCl$_3$)]; $R_f = 0.60$ ($n$-pentane/Et$_2$O 95:5, v/v); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.86 (t, $J = 7.2$ Hz, 3H), 1.12-1.20 (m, 1H), 1.22 (d, $J = 7.6$ Hz, 3H), 1.23...
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(t, $J = 7.2$ Hz, 3H), 1.34-1.42 (m, 1H), 2.13-2.21 (m, 1H), 2.44-2.56 (m, 2H), 2.80-2.88 (m, 1H), 2.85 (q, $J = 7.6$ Hz, 2H), 7.18-7.30 (m, 5H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 11.2, 14.7, 17.4, 23.3, 24.0, 41.3, 43.3, 45.3, 126.0, 127.8, 128.2, 145.4, 199.6; MS (EI) $m/z$ 250 (M$^+$, 16), 189 (100), 146 (36), 105 (78); HRMS Calcd. for C$_{15}$H$_{22}$OS 250.1391, found 250.1404.

Diastereoisomeric ratio was determined by chiral GC analysis, Chiralsil G-TA (25 m x 0.25 mm), initial temp. 75 °C, gradient: 3 °C/min; retention times (min): 32.0 (syn) and 32.6 (anti). Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H, n-heptane/i-PrOH, 99/1, v/v, 40 °C), retention times (min): 9.25 (3'S,4'S) and 10.76 (3'R,4'R).

(+)-S-Ethyl (3'R,4'S)-3-ethyl-4-phenylpentanethioate (syn-21b):

The same procedure as for anti-21a however using EtMgBr instead of MeMgBr and using (S)-L4 instead of (R)-L4. The reaction afforded a mixture of syn and anti isomers [58% yield, 28% de, >99.5% ee (major diastereomer), [α]$_D$ = +12.2 (c 1.0, CHCl$_3$)]; $R_f$ = 0.57 (n-pentane/Et$_2$O 95:5, v/v); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.88 (t, $J = 7.2$ Hz, 3H), 1.21 (t, $J = 7.6$ Hz, 3H), 1.25 (d, $J = 7.2$ Hz, 3H), 1.34-1.46 (m, 2H), 2.15-2.20 (m, 1H), 2.33-2.54 (m, 2H), 2.74-2.83 (m, 1H), 2.83 (q, $J = 7.2$ Hz, 2H), 7.17-7.30 (m, 5H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 10.4, 14.8, 17.8, 22.6, 23.3, 41.5, 43.1, 46.0, 126.1, 127.8, 128.3, 145.5, 199.6; MS (EI) $m/z$ 250 (M$^+$, 18), 189 (100), 146 (47), 105 (78), 91 (24); HRMS Calcd. for C$_{15}$H$_{22}$OS 250.1391, found 250.1396. Diastereoisomeric ratio was determined by chiral GC analysis, Chiralsil G-TA (25 m x 0.25 mm), initial temp. 75 °C, gradient: 3 °C/min; retention times (min): 32.0 (syn) and 32.6 (anti). Enantiomeric excess was determined on a derivative of syn-21b, the methyl oxoester syn-19b: A solution of a sample of syn-21b in MeOH was stirred with K$_2$CO$_3$ (ca. 10 equiv) at rt for 3 h. The mixture was concentrated in vacuo and the residu taken up in H$_2$O, which was extracted with Et$_2$O. GC analysis was performed on a crude sample of the methyl oxoester: CP Chiralsil Dex CB column (25m x 0.25mm), initial T = 70 °C, gradient: 3 °C / min to 110 °C, 110 °C isothermic, retention times (min): 78.5 (3'S,4'R), 80.3 (3'R,4'S).
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(+)-S-Ethyl (3R,4S)-3-methyl-4-phenyl-thiohexanoate (syn-21c):

The same procedure as for anti-21a however using 17e (contaminated with 18) instead of 17c and using (S)-L4 instead of (R)-L4. The reaction afforded a mixture of syn and anti isomers and the product of 18, which could be separated by column chromatography. [71% yield, 76% de, >99.5% ee (major diastereomer), [α]D = +5.0 (c 0.4, CHCl3)]; Rf = 0.63 (n-pentane/Et2O 95:5, v/v); 1H NMR (400 MHz, CDCl3): δ 0.71 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.52-1.62 (m, 1H), 1.78-1.87 (m, 1H), 2.13 (dd, J = 14.4 and 9.6 Hz, 1H), 2.27-2.32 (m, 2H), 2.44 (dd, J = 14.4 and 3.2 Hz, 1H), 2.83 (q, J = 7.2 Hz, 2H) 7.11-7.30 (m, 5H); 13C NMR (50 MHz, CDCl3): δ 12.2, 14.8, 17.6, 23.2, 25.1, 36.2, 49.4, 53.1, 126.2, 128.2, 143.3, 199.5; MS (EI) m/z 250 (M+, 10), 189 (100), 146 (30), 105 (43), 91 (41); HRMS Calcd. for C15H22OS 250.1391, found 250.1401. Diastereoisomeric ratio was determined by chiral GC analysis, Chiralsil G-TA (25 m x 0.25 mm), initial temp. 75 ºC, gradient: 3 ºC/min; retention times (min): 31.6 (syn) and 32.10 (anti). Alternatively, the dr was determined by 1H NMR spectroscopy, by comparison of the CHCH3 signals (0.78 ppm for anti, 0.99 ppm for syn). Enantiomeric excess was determined on a derivative of syn-21c, the methyl oxoester (3R,4S)-methyl 3-methyl-4-phenylhexanoate: A solution of a sample of syn-21c in MeOH was stirred with K2CO3 (ca. 10 equiv) at rt for 3 h. The mixture was concentrated in vacuo and the residu taken up in H2O, which was extracted with Et2O. GC analysis was performed on a crude sample of the methyl oxoester: CP Chiralsil Dex CB column (25m x 0.25mm), initial T = 70 °C, gradient: 3 °C / min to 110 °C, 110 °C isothermic, retention times (min): 70.9 (3R,4S), 73.0 (3S,4R).

(+)-S-Ethyl (3S,4S)-3-methyl-4-phenyl-thiohexanoate (anti-21c):

In a Schlenk tube CuBr-(R,S)-L1 (9.0 µmol, 6.60 mg) was dissolved in t-BuOMe (1.0 mL) and stirred under a N2-atmosphere at room temperature for 10 min. The mixture was cooled to −75 ºC and MeMgBr (3.0 M in Et2O, 0.45 mmol) was added dropwise. After stirring for 5 min at that temperature a solution of 17e (33.0 mg, 0.15 mmol) in t-BuOMe (1.0 mL) was added dropwise over 10 min. After stirring for 40 h at −75 ºC, MeOH (0.25 mL) andaq. NH4Cl (1M, 2
mL) were added sequentially, and the mixture was warmed to rt. After extraction with Et₂O (0.5 mL, 3x), the combined organic layers were dried and concentrated to a yellow oil, which was subjected to flash chromatography (silica gel, n-pentane/Et₂O 99.75:0.25, v/v) to afford a mixture of syn-21c and anti-21c. [67% yield, 96% de, >99.5% ee (major diastereomer), [α]D = +19.1 (c 0.8, CHCl₃); Rf = 0.65 (pentane/Et₂O 95:5, v/v); ¹H NMR (400 MHz, CDCl₃): δ 0.74 (t, J = 7.2 Hz, 3H), 0.78 (d, J = 6.4 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.65-1.75 (m, 2H), 2.24 (dd, J = 14.4 and 8.8 Hz, 1H), 2.30-2.40 (m, 2H), 2.65 (dd, J = 14.4 and 4.8 Hz, 1H), 2.88 (q, J = 7.2 Hz, 2H) 7.10-7.30 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 12.4, 14.8, 16.6, 23.3, 25.7, 35.6, 49.6, 52.4, 126.0, 128.0, 128.9, 142.3, 199.4; MS (EI) m/z 250 (M⁺, 10), 189 (100), 146 (30), 105 (40), 91 (43); HRMS Calcd. for C₁₅H₂₂OS 250.1391, found 250.1403. Diastereoisomeric ratio was determined by chiral GC analysis, Chiralsil G-TA (25 m x 0.25 mm), initial temp. 75 °C, gradient: 3 °C/min; retention times (min): 31.6 (syn) and 32.1 (anti). Alternatively, the dr was determined by ¹H NMR spectroscopy, by comparison of the CHCH₃ signals (0.78 ppm for anti, 0.99 ppm for syn). Enantiomeric excess was determined on a derivative of anti-21c, the methyl oxoester (3S,4S)-methyl 3-methyl-4-phenylhexanoate: A solution of a sample of anti-21c in MeOH was stirred with K₂CO₃ (ca. 10 equiv) at rt for 3 h. The mixture was concentrated in vacuo and the residue taken up in H₂O, which was extracted with Et₂O. GC analysis was performed on a crude sample of the methyl oxoester: ChiralDEX G-TA column (30m x 0.25mm), initial T = 70 °C, gradient: 2 °C / min to 90 °C, 90 °C isothermic, retention times (min): 133.2 (3R,4R), 137.1 (3S,4S).

(−)-Methyl (E,4S)-5-(benzylxylo)-4-methyl-2-pentenoate (35):⁶⁰

In a dried Schlenk tube, under a N₂-atmosphere Hoveyda-Grubbs 2nd generation catalyst (50 μmol, 31.5 mg) was added to a solution of methyl acrylate 16a (12.5 mmol, 1.1 mL) and 27 (2.5 mmol, 440 mg) in CH₂Cl₂ (5 mL). The resulting green solution was stirred for 20 h at rt. The mixture was then concentrated in vacuo and the residue purified by flash chromatography (SiO₂, 2 : 98 to 5 : 95 Et₂O / n-pentane gradient, Rf (5:95) = 0.2), which afforded 35 (479 mg) as a colorless oil. [82% yield, 94% ee, [α]D = −16.4 (c 1.9, CHCl₃); lit.⁶⁰ [α]D = +15.0 (c 3.02, CHCl₃, (R)-35)]; ¹H-NMR δ 7.37-7.26 (m, 5H), 6.96
(dd, J = 15.8 and 7.1 Hz, 1H), 5.87 (dd, J = 15.8 and 1.4 Hz, 1H), 4.51 (s, 2H), 3.73 (s, 3H), 3.44-3.36 (m, 2H), 2.72-2.61 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H); 13C-NMR δ 167.1, 151.5, 138.1, 128.3, 127.6, 127.6, 120.5, 73.9, 73.1, 51.4, 36.8, 16.0; MS (EI) m/z 234 (M+, 0.6), 113 (9), 92 (9), 91 (100), 65 (6); HRMS Calcd. for C14H18O3 234.1256, found 234.1267. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD (98% n-heptane/i-PrOH), 40°C, retention times (min): 6.9 (S-enantiomer) and 9.2 (R-enantiomer).

(−)-S-Ethyl (E,4S)-(2)-5-(benzyloxy)-4-methyl-2-pentenethioate (28): 61

Route A, from the methyl ester 35: To a solution of 35 (3.07 mmol, 720 mg) in THF (10 mL) in a dry Schlenk tube, under a N2-atmosphere, AlCl3 (3.6 mmol, 480 mg) and Et3SiMe3 (6.0 mmol, 970 μL) were added sequentially. The resulting solution was heated at reflux temperature for 16 h, after which the reaction was quenched with an aq. phosphate buffer solution (pH = 7, 12.5 mL). The mixture was extracted with Et2O (15 mL, 3x) and the combined organic layers were dried (MgSO4) and concentrated in vacuo. The residue was purified by flash chromatography (SiO2, 5 : 95 tBuOMe / pentane, Rt = 0.5), which afforded 28 as a colorless oil (695 mg, 86% yield).

Route B, from the terminal olefin 27: In a dry Schlenk tube, under a N2-atmosphere Hoveyda-Grubbs 2nd generation catalyst (50 μmol, 31.3 mg) was added to a solution of S-ethyl thioacrylate 16c (2.0 mmol, 229 μL) and 27 (1.0 mmol, 176 mg) in CH2Cl2 (2.5 mL). The resulting green solution was heated for 6 h at reflux temperature. The mixture was allowed to cool, a second portion of the catalyst was added (50 μmol, 31.3 mg) and the mixture was heated for another 18 h at reflux temperature. The mixture was then concentrated in vacuo and purified by flash chromatography (SiO2, 5 : 95 Et2O / n-pentane, Rt = 0.5), which afforded an inseparable mixture of 28 and the side product 29 (236 mg, ratio 28:29 = 20:1, 83% corrected yield 28) as a colorless oil. [94% ee, [α]D = −17.6 (c 1.9, CHCl3)]; 1H-NMR δ 7.37-7.26 (m, 5H), 6.88 (dd, J = 15.7 and 7.0 Hz, 1H), 6.14 (dd, J = 15.7 and 1.4 Hz, 1H), 4.52 (s, 2H), 3.44-3.37 (m, 2H), 2.95 (q, J = 7.4 Hz, 2H), 2.69-2.61 (m, 1H), 1.28 (t, J = 7.4 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H); 13C-NMR δ 190.1, 146.9, 138.1, 128.3, 128.1, 127.4, 73.7, 73.1, 36.7, 23.1, 16.0, 14.8; MS (EI) m/z 264 (M+, 0.2), 235 (2), 203 (4), 174 (11), 145 (9), 117 (12), 92 (8), 91 (100),...
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83 (6), 82 (14), 65 (6); HRMS Calcd. for C\textsubscript{15}H\textsubscript{20}SO\textsubscript{2} 264.1187, found 264.1184. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OB-H (98\% \textit{n}-heptane/\textit{i}-PrOH), 40ºC, retention times (min): 20.7 (\textit{S}-enantiomer) and 26.3 (\textit{R}-enantiomer).

\((2\text{S},5\text{S},E)\)-1,6-dibenzyloxy-2,5-dimethylhex-3-ene (29):

In a dry Schlenk tube, under a N\(_2\)-atmosphere Hoveyda-Grubbs 2\textsuperscript{nd} generation catalyst (5.0 \(\mu\)mol, 3.13 mg) was added to a solution of 27 (0.5 mmol, 88 mg) in CH\(_2\)Cl\(_2\) (0.5 mL). The resulting green solution was stirred for 20 h at rt. The mixture was then concentrated in vacuo and purified by flash chromatography (SiO\(_2\), 0 : 100 to 5 : 95 Et\(_2\)O / \textit{n}-pentane gradient, \(R_f\) (5:95) = 0.5), which afforded 29 (64 mg, 80\% yield) as a colorless oil; \(^1\)H-NMR \(\delta\) 7.36-7.25 (m, 10H), 5.43 (dd, \(J = 4.0\) and 1.8 Hz, 2H), 4.51 (s, 4H), 3.37 (dd, \(J = 9.1\) and 6.3 Hz, 2H), 3.26 (dd, \(J = 9.1\) and 7.3 Hz, 2H), 2.52-2.43 (m, 2H), 1.03 (d, \(J = 6.8\) Hz, 6H); \(^1\)C-NMR \(\delta\) 138.6; 132.4; 128.2; 127.4; 127.3; 75.4; 72.8; 36.8; 17.2; MS (EI) \(m/z\) 324 (M\(^+\), 0.05), 234 (5), 233 (31), 97 (8), 96 (6), 92 (9), 91 (100), 65 (5); HRMS Calcd. for C\(_{22}\)H\(_{28}\)O\(_2\) 324.2089, found 324.2084.

\((+)-S\)-Ethyl (3\text{S},4\text{S})-5-(benzyloxy)-3,4-dimethyl-pentanethioate (\textit{anti}-23):

A dry Schlenk tube equipped with septum and stirring bar was charged with Cul (42 \(\mu\)mol, 8.0 mg), \((R)\)-Tol-BINAP (46 \(\mu\)mol, 31.2 mg) and \(t\)-BuOMe (11.0 mL) and stirred under a N\(_2\)-atmosphere at room temperature until a yellow colour appeared. The mixture was cooled to –70 °C, methyl Grignard reagent (5.6 mmol, 3M solution in Et\(_2\)O, 1.85 mL) was added dropwise and the mixture was stirred for 10 min. Unsaturated thioester 28 (contaminated with 29) (1.39 mmol, 94 wt\%, 391 mg) was added dropwise as a solution in 3.5 mL CH\(_2\)Cl\(_2\) at that temperature. The resulting mixture was stirred at –70 °C for 16 h. The reaction was quenched by addition of MeOH (2 mL) and sat. aqueous NH\(_4\)Cl solution (10 mL), the mixture was removed from the cooling bath and allowed to reach rt. Subsequently, enough H\(_2\)O to dissolve all salts and 15 mL Et\(_2\)O were added, the organic layer was separated and the resulting aqueous layer was extracted with Et\(_2\)O (2x 10 mL). The combined organic layers were dried (MgSO\(_4\)), filtered and concentrated in vacuo to yield a
yellow oil, which was purified by flash chromatography (SiO₂, 5 : 95 Et₂O / n-pentane, Rf = 0.35), affording *anti*-23 as a colorless oil (352 mg). [91% yield, 98 : 2 dr, >99.5% ee (major diastereomer), [α]₂⁰ = +5.1 (c 2.4, CHCl₃)]; ¹H-NMR δ 7.35-7.26 (m, 5H), 4.50 (s, 2H), 3.39 (dd, J = 9.3 and 6.5 Hz, 1H), 3.29 (dd, J = 9.3 and 6.4 Hz, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.62 (dd, J = 14.4 and 4.3 Hz, 1H), 2.35 (dd, J = 14.4 and 9.7 Hz, 1H), 2.28-2.18 (m, 1H), 1.87-1.76 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H); ¹³C-NMR δ 199.6, 138.6, 128.3, 127.5, 127.4, 73.2, 73.0, 47.8, 37.8, 32.9, 23.3, 16.8, 14.8, 13.9; MS (EI) m/z 280 (M⁺, 0.3), 219 (14), 92 (9), 91 (100); HRMS Calcd. for C₁₆H₂₄SO₂ 280.1497, found 280.1498. Enantiomeric excess and diastereomeric ratio were determined by chiral HPLC analysis, Chiralcel OB-H (99.7% n-heptane/i-PrOH), 40ºC, retention times (min): 25.4 (3R,4S), 29.0 (3S,4S [major]), 33.5 (3R,4R) and 38.1 (3S,4R).

(+)-5-Ethyl (3R,4S)-5-(benzyloxy)-3,4-dimethylpentanethioate (syn-23):

The same procedure as for *anti*-23 however using (S)-L₄ instead of (R)-L₄ and the reaction was performed at 0.25 mmol scale. Purification by flash chromatography (SiO₂, 5 : 95 Et₂O / n-pentane, Rf = 0.35) afforded *syn*-23 as a colorless oil (59.5 mg). [85% yield, 96 : 4 dr, >99.5% ee (major diastereomer), [α]₂⁰ = +5.8 (c 3.7, CHCl₃)]; ¹H-NMR δ 7.37-7.25 (m, 5H), 4.52-4.45 (m, 2H), 3.37 (dd, J = 9.3 and 6.7 Hz, 1H), 3.28 (dd, J = 9.3 and 6.6 Hz, 1H), 2.87 (q, J = 7.4 Hz, 2H), 2.58 (dd, J = 14.4 and 5.6 Hz, 1H), 2.40 (dd, J = 14.4 and 8.8 Hz, 1H), 2.35-2.24 (m, 1H), 1.89-1.80 (m, 1H), 1.24 (t, J = 7.4 Hz, 3H), 0.86 (d, J = 5.4 Hz, 3H), 0.84 (d, J = 5.3 Hz, 3H); ¹³C-NMR δ 199.2, 138.5, 128.3, 127.5, 127.4, 73.7, 72.9, 49.3, 36.8, 32.0, 23.2, 14.8, 14.6, 12.2; MS (EI) m/z 219 (12), 113 (5), 92 (11), 91 (100); HRMS Calcd. for C₁₆H₂₃O₂ [M−SEt]⁺ 219.1385, found 219.1387. Enantiomeric excess and diastereomeric ratio were determined by chiral HPLC analysis, Chiralcel OB-H (99.7% n-heptane/i-PrOH), 40ºC, retention times (min): 25.4 (3R,4S [major]), 29.0 (3S,4S), 33.5 (3R,4R) and 38.1 (3S,4R).
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(+)-(3S,4S)-5-(Benzyloxy)-3,4-dimethylpentanal (30):

Thioester anti-23 (0.36 mmol, 101 mg) was dissolved in CH₂Cl₂ (3.5 mL) under a N₂-atmosphere in a dry Schlenk tube equipped with stirring bar and septum. The solution was cooled down to −55 °C and a solution of diisobutylaluminumhydride (0.55 mmol, 1.0 M in CH₂Cl₂, 0.55 mL) was added dropwise. After stirring at −55 °C for 2 h, a sat. aqueous solution of Rochelle salt (5 mL) was added and the resulting mixture was stirred vigorously at rt for 1 h. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2x 5 mL). The combined organic layers were washed with brine (1 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, 10 : 90 Et₂O / n-pentane, R_f = 0.35), which afforded 30 as a colorless oil (76 mg). [96% yield, [α]D = +14.7 (c 1.4, CHCl₃)]; ¹H-NMR δ 9.72 (dd, J = 2.9 and 1.6 Hz, 1H), 7.37-7.26 (m, 5H), 4.50 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.36 (dd, J = 9.3 and 7.0 Hz, 1H), 3.32 (dd, J = 9.4 and 6.0 Hz, 1H), 2.46 (dd, J = 15.9, 4.3 and 1.4 Hz, 1H), 2.35-2.25 (m, 1H), 2.17 (dd, J = 15.8, 9.2 and 2.9 Hz, 1H), 1.89-1.78 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H); ¹³C-NMR δ 203.0, 138.4, 128.3, 127.5, 127.5, 73.1, 73.0, 47.3, 37.8, 29.5, 17.6, 13.5; MS (EI) m/z 220 (M⁺, 5), 177 (6), 129 (7), 113 (22), 111 (6), 108 (27), 107 (32), 96 (7), 95 (6), 92 (35), 91 (100), 83 (12), 81 (11), 79 (6), 77 (7), 71 (20), 70 (8), 69 (15), 65 (13); HRMS Calcd. for C₁₄H₂₀O₂ 220.1463, found 220.1455.

(+)-Benzyl (2S,3S)-2,3,6-trimethyl-5-heptenyl ether (31):

In a dry Schlenk tube equipped with septum and stirring bar, isopropyltriphenylphosphonium iodide (1.33 mmol, 577 mg) was suspended in THF (8.5 mL) under a N₂-atmosphere and cooled to 0 °C. A solution of n-BuLi (1.33 mmol, 1.6 M in hexanes, 0.83 mL) was added dropwise and the mixture was stirred at 0 °C for 15 min. The resulting red mixture was cooled down to −78 °C and stirred 15 min at this temperature, after which a solution of aldehyde 30 (0.43 mmol, 94.9 mg) in THF (4.5 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 60 min, then at 0 °C for 1.5 h and then a sat. aqueous solution of NH₄Cl (1 mL) was added. The mixture was diluted with EtOAc (20 mL) and washed with a sat. aqueous solution of NH₄Cl (2x 5
mL). The organic layer was dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, 1 : 99 Et₂O / n-pentane, Rf = 0.55), which afforded 31 as a colorless oil (95 mg). [90% yield, [α]D = +8.4 (c 2.1, CHCl₃)]; ¹H-NMR δ 7.36-7.25 (m, 5H), 5.12 (t, J = 7.2 Hz, 1H), 4.50 (s, 2H), 3.46 (dd, J = 9.1 and 5.7 Hz, 1H), 3.29 (dd, J = 9.1 and 7.3 Hz, 1H), 2.06-1.99 (m, 1H), 1.86-1.74 (m, 2H), 1.70 (s, 3H), 1.59 (s, 3H), 1.63-1.54 (m, 1H), 0.94 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ¹³C-NMR δ 138.8, 131.8, 128.3, 127.5, 127.4, 123.8, 73.8, 73.0, 37.8, 35.8, 31.5, 25.8, 17.8, 16.9, 14.4; MS (EI) m/z 247 (7), 246 (M⁺, 38), 175 (14), 155 (9), 138 (8), 137 (42), 97 (23), 96 (11), 95 (10), 92 (12), 91 (100), 83 (10), 81 (17), 71 (6), 70 (6), 69 (53), 65 (7), 57 (10), 55 (16); HRMS Calcd. for C₁₇H₂₆O₂ 246.1984, found 246.1979.

(2S,3S)-2,3,6-trimethyl-5-hepten-1-ol [(-)-Lasiol] (22): Liquid NH₃ was condensed in a dry Schlenk flask under a N₂-atmosphere at −78 °C. A second dry Schlenk flask under N₂ was equipped with septum and stirbar, charged with pieces of Li (5.8 mmol, 40 mg) and THF (3.0 mL) and also cooled to −78 °C. The flasks were connected via cannula and the flask with NH₃ was removed from the cooling bath allowing the NH₃ (ca. 10 mL) to distill into the second flask. After stirring at −78 °C for 30 min a solution of 31 (0.34 mmol, 84.3 mg) in THF (2.0 mL) was added dropwise to the dark blue solution. After 20 min solid NH₄Cl (1.5 g) was added carefully and the NH₃ was allowed to evaporate using a water bath at rt. A sat. aqueous solution of NaCl (10 mL) was added and just enough H₂O to dissolve all the salts. The organic layer was separated and the resulting water layer was extracted with Et₂O (3x, 15 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, 20 : 80 Et₂O / n-pentane, Rf = 0.4) affording (−)-lasiol 22 as a colorless liquid (52 mg). [99% yield, [α]D = −10.2 (c 1.9, n-hexane); lit. [(−)-Lasiol] 46b [α]D = −12.1 (c 0.995, n-hexane)]; ¹H-NMR δ 5.12 (br t, J = 7.2 Hz, 1H), 3.65 (dd, J = 10.6 and 5.4 Hz, 1H), 3.46 (dd, J = 10.6 and 7.1 Hz, 1H), 2.00-2.07 (m, 1H), 1.84-1.51 (m, 10H, containing two singlets of each 3H: 1.70 and 1.60 ppm), 0.93 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 1H); ¹³C-NMR δ 132.0, 123.5, 66.0, 40.2, 35.4, 31.3, 25.8, 17.7, 16.9, 13.7; MS (EI) m/z 156 (M⁺, 38), 139 (7), 138 (10), 137 (9), 125 (6), 123 (33), 109 (19), 97
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(21), 96 (34), 95 (25), 86 (6), 85 (32), 83 (13), 82 (24), 81 (21), 71 (16), 70 (55), 69 (100), 68 (12), 67 (16), 59 (10), 58 (7), 57 (19), 56 (17), 55 (46), 53 (11); HRMS Calcd. for C_{10}H_{20}O 156.1514, found 156.1519.

(+)-2-((2S,3S)-4-(Benzyloxy)-2,3-dimethylbutyl)-1,3-dioxolane (32): A catalytic amount of $p$-TsOH·H_2O (0.26 mmol, 50 mg) was added to a stirred suspension of aldehyde 30 (4.7 mmol, 1.04 g), ethylene glycol (30 mmol, 1.5 mL) and 5.0 g MgSO_4 in 60 mL benzene. The mixture was heated at reflux temperature for 14 h, after which it was diluted with 50 mL Et_2O and filtered. The filtrate was washed with sat. aq. NaHCO_3 (40 mL) and brine (20 mL), dried with MgSO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 10 : 90 Et_2O / n-pentane, R_f = 0.25), affording 32 as a colorless oil (1.19 g). [95 % yield, [α]_D = +3.0 (c 5.2, CHCl_3)]; 1H-NMR δ 7.36-7.25 (m, 5H), 4.89 (dd, J = 5.9 and 4.4 Hz, 1H), 4.49 (s, 2H), 3.99-3.91 (m, 2H), 3.89-3.80 (m, 2H), 3.42 (dd, J = 9.2 and 6.0 Hz, 1H), 3.27 (dd, J = 9.2 and 7.0 Hz, 1H), 1.90-1.76 (m, 2H), 1.69 (ddd, J = 13.8, 5.9 and 3.8 Hz, 1H), 1.47 (ddd, J = 14.0, 9.8 and 4.4 Hz, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); 13C-NMR δ 138.7, 128.2, 127.4, 127.3, 104.1, 73.4, 72.9, 64.7, 64.5, 38.3, 36.9, 31.0, 17.1, 13.6; MS (EI) m/z 264 (M^+, 0.8), 173 (6), 157 (10), 115 (11), 113 (14), 107 (7), 97 (6), 96 (6), 92 (7), 91 (54), 73 (100), 65 (6); HRMS Calcd. for C_{16}H_{24}O_{3} 264.1726, found 264.1735.

(−)-(2S,3S)-4-(1,3-Dioxolan-2-yl)-2,3-dimethylbutan-1-ol (33): A suspension of benzyl ether 32 (0.3 mmol, 79 mg) and Pd(OH)_2/C (15 μmol, 60 wt% (moist), dry: 20 wt% Pd(OH)_2, 26 mg) in EtOAc (3.0 mL) was stirred vigorously at rt under a H_2-atmosphere for 30 min. Celite was added and the suspension was filtered over Celite. The filtrate was washed with EtOAc and the combined filtrates were concentrated. The residue was purified by flash chromatography (SiO_2, 20 : 80 to 100 : 0 Et_2O / n-pentane gradient, R_f (70:30) = 0.35), affording 33 as a colorless oil (52 mg). [99% yield, [α]_D = −20.3 (c 2.4, CHCl_3)]; 1H-NMR δ 4.86 (dd, J = 6.2 and 3.6 Hz, 1H), 3.97-3.88 (m, 2H), 3.86-3.78 (m, 2H), 3.49 (dd, J = 11.0 and 7.4 Hz, 1H), 3.39 (dd, J = 11.0 and 6.5 Hz, 1H), 2.38 (br s, 1H), 1.89-
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1.79 (m, 1H), 1.69-1.59 (m, 2H), 1.45-1.38 (m, 1H), 0.94 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H); 13C-NMR δ 103.9, 65.1, 64.5, 64.4, 40.2, 35.7, 29.5, 17.7, 12.2; MS (EI) m/z 173 ([M−H]+, 4), 115 (8), 113 (7), 102 (10), 88 (13), 85 (5), 74 (12), 73 (100), 71 (8), 69 (7), 55 (8); MS (CI) m/z 193 (11), 192 ([M+NH₄]+, 100), 175 ([M+H]+, 6), 147 (12), 131 (6), 130 (62), 113 (16); HRMS Calcd. for [M−H]+ C₉H₁₇O₃ 173.1178, found 173.1185.

(+)-2-((2S,3S)-4-Iodo-2,3-dimethylbutyl)-1,3-dioxolane (25):

To a stirred solution of alcohol 33 (0.27 mmol, 46 mg), PPh₃ (0.4 mmol, 105 mg) and imidazole (0.5 mmol, 34 mg) in benzene (2.0 mL) and DMF (0.1 mL), I₂ (0.45 mmol, 114 mg) was added in one portion. The resulting mixture was stirred at rt for 45 min, after which it was poured into 5 mL sat. aq. Na₂S₂O₃ solution and extracted with Et₂O (5 mL, 2x). The combined organic layers were dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (SiO₂, 5 : 95 Et₂O / n-pentane, Rf = 0.25), affording 25 as a colorless oil (69 mg). [91% yield, [α]D = +1.3 (c 3.2, CHCl₃)]; ¹H-NMR δ 4.89 (dd, J = 5.8 and 4.3 Hz, 1H), 4.00-3.92 (m, 2H), 3.89-3.81 (m, 2H), 3.27 (dd, J = 9.7 and 4.7 Hz, 1H), 1.85-1.76 (m, 1H), 1.68 (ddd, J = 13.7, 5.7 and 3.8 Hz, 1H), 1.64-1.56 (m, 1H), 1.48 (ddd, J = 13.9, 9.6 and 4.3 Hz, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ¹³C-NMR δ 103.6, 64.7, 64.5, 40.5, 36.5, 33.5, 17.1, 17.1, 14.2; MS (EI) m/z 283 (7), 157, (8), 95 (7), 73 (100); MS (CI) m/z 302 ([M+NH₄]+, 17), 69 (100); HRMS Calcd. for [M−H]+ C₉H₁₆O₂I 283.0195, found 283.0248.

(−)-2-((2S,3S,5E,9Z)-2,3,6,10-Tetramethyl-dodeca-5,9-dienyl)-1,3-dioxolane (34):

A dry Schlenk tube equipped with septum and stirring bar was charged with alkyl iodide 25 (232 μmol, 66 mg) and Et₂O (1.2 mL) under a N₂-atmosphere and cooled to −78 °C. Via syringe i-BuLi (0.51 mmol, 1.9 M soln. in pentane, 0.27 mL) was added dropwise and the solution was stirred at −78 °C for 20 min. A solution of dried ZnBr₂ (0.29 mmol, 65 mg) in THF (0.7 mL) was added dropwise via syringe and the resulting mixture was allowed to warm to 0 °C in 1 h. At 0
°C a solution of (1E,5Z)-1-iodo-2,6-dimethylocta-1,5-diene 24 (0.35 mmol, 92 mg) and [Pd(dppf)Cl₂]-CH₂Cl₂ (11.6 μmol, 9.5 mg) in a mixture of THF / DMF (0.8 mL, 1 : 1) was added via syringe and the resulting green suspension was stirred at rt for 16 h. H₂O (5 mL) was added to the mixture, which was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, 1 : 99 to 2 : 98 Et₂O / n-pentane gradient, Rf (1 : 99) = 0.1), affording 34 as a colorless oil (48 mg). [71% yield, [α]D = −3.8 (c 0.9, CHCl₃); ¹H-NMR δ 5.12 (br t, J = 6.7 Hz, 1H), 5.06 (br t, J = 6.5 Hz, 1H), 4.88 (dd, J = 5.8 and 4.4 Hz, 1H), 4.00-3.91 (m, 2H), 3.89-3.80 (m, 2H), 2.10-1.95 (m, 7H), 1.83-1.75 (m, 1H), 1.74-1.67 (m, 2H), 1.66 (dd, J = 2.4 and 1.2 Hz, 3H), 1.58 (s, 3H), 1.40-1.42 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H), 0.93 (d, J = 6.1 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H); ¹³C-NMR δ 136.9, 135.3, 123.9, 123.7, 104.3, 64.7, 64.5, 40.1, 38.8, 37.1, 33.5, 31.3, 26.2, 24.7, 22.8, 16.8, 16.0, 15.9, 12.8; MS (EI) m/z 294 (M⁺, 4), 149 (6), 123 (7), 121 (5), 115 (7), 114 (6), 113 (100), 107 (16), 95 (15), 93 (6), 83 (21), 81 (16), 73 (66), 69 (10), 67 (10), 55 (44); HRMS Calcd. for C₁₉H₃₄O₂ 294.2559, found 294.2550.

(3S,4R,6E,10Z)-3,4,7,11-tetramethyl-trideca-6,10-dienal [(+)

In a Schlenk flask under a N₂-atmosphere dioxolane 34 (63 μmol, 18.5 mg) was dissolved in a mixture of THF and water (24 mL, 5 : 1). p-TsOH·H₂O (1.26 mmol, 240 mg) was added and the solution was heated at reflux temperature for 1 h. The mixture was poured into sat. aqueous NaHCO₃ (20 mL) and extracted with 40 mL Et₂O. The organic layer was subsequently washed with sat. aqueous NaHCO₃ (10 mL) and brine (10 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, 2 : 98 Et₂O / n-pentane, Rf = 0.2), affording 3 as a colorless oil (9.7 mg). [62% yield, [α]D = +19.2 (c 1.0, CHCl₃); lit. ¹³C-NMR δ 9.74 (dd, J = 1.7 and 2.6 Hz, 9H), 5.11 (br t, J = 6.7 Hz, 1H), 5.05 (br t, J = 6.6 Hz, 1H), 2.47-2.41 (m, 1H), 2.21-1.95 (m, 9H), 1.87-1.78 (m, 1H), 1.66 (s, 3H), 1.58 (s, 3H), 1.52-1.42 (m, 1H), 0.96 (t, J = 7.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); ¹³C-NMR δ 203.3, 137.1, 135.9, 123.8, 123.0, 47.4, 40.1, 38.4,
32.0, 31.8, 26.2, 24.7, 22.8, 17.5, 16.1, 15.9, 12.8; MS (EI) m/z 250 (M+, 6), 203 (5), 194 (7), 193 (44), 177 (5), 175 (12), 149 (9), 138 (6), 137 (23), 136 (6), 124 (5), 123 (29), 122 (7), 121 (9), 111 (8), 109 (13), 107 (17), 99 (6), 97 (9), 96 (7), 95 (20), 93 (9), 84 (8), 83 (100), 82 (23), 81 (27), 79 (6), 69 (20), 68 (7), 67 (17), 57 (5), 55 (87), 53 (7); HRMS Calcd. for C_{17}H_{30}O \: 250.2297, \text{found 250.2307.}
References:


Chapter 4


Catalytic enantioselective synthesis of vicinal dialkyl arrays


38 van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 5651-5653; see also chapter 5.

39 All conjugate additions with substrates 17d and 17e were performed on their mixtures with 18. The conjugate addition products of 18 were separated by column chromatography from the products of 17.

40 Recently, Loh and coworkers reported that the use of MeMgBr was possible under certain reaction conditions with their catalyst system: Wang, S.-Y.; Lum, T.-K.; Ji, S.-J.; Loh, T.-P. *Adv. Synth. Catal.* **2008**, *350*, 673-677; see also reference 34.

41 Extended reaction times to allow completion of the reaction did not improve the yield, but did lead to a reduction in diastereoselectivity and enantiomeric excess.

42 We cannot explain the different extents of racemization using MeMgBr and using EtMgBr. A difference in basicity has never been reported. However, it is known that the reagents have different Schlenk equilibria in some solvents. See: *The Chemistry of Organomagnesium Compounds* Eds.: Rappoport, Z.; Marek, I. **2008**, Wiley, Chichester.

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54 The dimer 29 could not be separated from 28. It could be separated from the product of the following conjugate addition, however. Pure 28 could be obtained via cross-metathesis with methyl acrylate (product 35) followed by transesterification. For this route and the separate synthesis and characterization of 29, see Experimental Part.

55 Despite selective syntheses of both enantiomers of lasiol, the absolute configuration of the natural compound has not been established.

56 Certain reaction conditions, such as extended reaction times or the use of Pd/C as the catalyst, led to the formation of a complex mixture of products, probably due to partial trans-acetalization. For precedents, see: a) Andrey, O.; Vidonne, A.; Alexakis, A. Tetrahedron Lett. 2003, 44, 7901-7904; b) Börjesson, L.; Csöregh, I.; Welch, C. J. J. Org. Chem. 1995, 60, 2989-2999.


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59 Optical rotation measured of the product of a reaction with reaction time 3 h, which had lower conversion and yield.

