Copper-catalysed asymmetric carbon-carbon bond formation using Grignard reagents

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Chapter 5

Enantiopure allylic alcohols: the development of the copper-catalysed hetero-allylic asymmetric alkylation ($h$-AAA) reaction with Grignard reagents

Part of this chapter has been published:

5.1 Introduction

Research in our group directed at expanding and diversifying the scope and utility of asymmetric conjugate additions (ACA)\(^1\,^2\) reactions to enones\(^3\), esters\(^4\) and thioesters\(^5\) led to the development of tandem sequential 1,4-addition enolate trapping procedures.\(^6\) In particular the development of tandem consecutive 1,4-addition-Ireland–Claisen (I.C.) rearrangement protocols, as discussed in chapter 3, for the construction of chiral 1,2-dialkyl arrays 5.2 proved to be challenging (Scheme 1). Based on our observations and precedent literature,\(^7\) it became clear that an stereoegenic centre in position b (see Scheme 1) that is involved in the rearrangement was required to induce high levels of stereoselectivity during rearrangement instead of a stereoegenic centre present at position a (Scheme 1).

![Scheme 1: Retrosynthesis of tandem consecutive 1,4-addition-I.C. substrates.](image)

This motivated us to gain access to molecules with a structural motive like compound 5.3 (Scheme 1). Retrosynthesis of compound 5.3 identifies two possible starting materials, acid chloride 5.4 (R\(^1\) = Ph) and chiral allylic alcohol 5.5. The nature of the R groups of the allylic alcohol is determined by the restrictions that the 1,4-addition method imposes on the steric parameters of the ester moiety. It is known that using more bulky esters results in lower enantioselectivity in the 1,4-addition to \(\alpha,\beta\)-unsaturated esters.\(^4\) Therefore the chiral allylic alcohol should be as small as possible, i.e. R\(^2\) = H, R\(^3\) = Me.

5.1.1 Enantiomerically pure low molecular weight allylic alcohols

Enantiomerically pure allylic alcohols 5.5 and their derivatives are key building blocks in numerous synthetic applications.\(^8\) Besides a number of multistep routes, catalytic methods have been developed involving (dynamic) kinetic resolution\(^9\) or enantioselective addition of alkenyl zinc\(^10\) and boron\(^11\) reagents to carbonyl compounds. Recent breakthroughs for the preparation of optically active allylic alcohol derivatives are based on transition–metal catalysed allylic substitution using oxygen nucleophiles. Most of these processes give allylic ethers.\(^12,\,13\) However, the chemoselective removal of, for instance, the \(O\)-benzyl ether
protecting group from the allylic alcohol products is difficult because of the presence of the terminal olefinic bond as well as the potential for undesired hydrogenolysis of the benzyllic/allylic C–O bond that defines the stereogenic centre. However Overman and co-workers were the first to successfully address this issue with the use of carboxylic acids as nucleophiles in the conversion of (Z)-allylic trichloroacetimidates 5.6 and 5.7 to allylic esters in high yield and excellent selectivities (Scheme 2).

Scheme 2: Pd(II) catalysed synthesis of chiral allylic esters.

Carreira et al reported the iridium-catalysed enantioselective allylation using silanolates as nucleophiles (Scheme 3).14

Scheme 3: Iridium catalysed asymmetric synthesis of chiral allylic alcohols.

This transformation yields TES-ethers that can easily be deprotected to the corresponding alcohol without loss of enantioselectivity. The catalytic asymmetric methods reported above do not provide access to low molecular weight allylic alcohols 5.5 when R < Ethyl and R1 < Me. In addition, successful kinetic resolution of low molecular weight allylic alcohols are conspicuously absent in reviews of the Sharpless epoxidation.16

Scheme 4: Unsuccessful routes to low molecular weight allylic alcohols.
The only viable synthetic route to low-molecular weight allylic alcohols is multistep synthesis using stoichiometric reagents from the chiral pool. The goal of the research described in this chapter is therefore the development of a catalytic asymmetric route towards the preparation of enantiopure protected secondary allylic alcohols via asymmetric C-C bond formation.

5.2 Retrosynthesis of chiral allylic alcohols

As mentioned above, chiral allylic alcohols have thus far been synthesized via catalytic asymmetric synthesis using two different approaches: allylic substitution using oxygen nucleophiles (Fig 1, 1) and 1,2-addition to aldehydes (Fig 1, 2).

![Figure 1: Retrosynthesis of chiral allylic alcohols.](image)

Building on previous experiences with Cu-catalysed allylic substitution reactions with Grignard nucleophiles on functionalized substrates (Fig 2, R = OBn, OTBDPS, X= Br) the construction of allylic esters might be feasible through a Cu-catalysed hetero-allylic asymmetric alkylation (h-AAA) with Grignard nucleophiles (Fig 1, 3). In this context it should be noted that Trost and Lee reported asymmetric Pd-catalysed allylic substitutions of geminal dicarboxylates using soft carbon nucleophiles. Prime candidate substrates for this new transformation would obviously be protected 3-bromopropenyl alcohols (Fig 2, 5.15). However the right 'type' of protecting group (R) would need to be found, since 5.15 contains a leaving group with a neighbouring vinylogous oxygen functionality (enol ether) so R would need to be sufficiently electron withdrawing for the substrate to be stable.
Furthermore, the protecting group R needs to be compatible with highly reactive RMgBr species. Finally, substrate 5.15 should also be readily available. We chose to explore 3-bromopropenyl esters (Fig 2, 5.15, R = PhCO, X = Br), available through simple condensation of an acyl bromide and a α,β-unsaturated aldehyde.\textsuperscript{21} Even though ester groups are prone to be attacked by Grignard reagents in a 1,2-addition fashion, we anticipated that the use of low temperature and an appropriate catalytic system would allow the selective alkylation in the presence of an ester moiety. This seemed reasonably given the successful 1,4-addition to α,β-unsaturated esters.\textsuperscript{4} The overall reaction with conditions derived from previous research,\textsuperscript{18} for the Cu-catalysed h-AAA with Grignard reagents on 3-bromopropenyl esters is depicted in Scheme 5.

Scheme 5: Cu-catalysed h-AAA with Grignard reagents.

### 5.3 Synthesis of 3-bromopropenyl esters

3-Bromopropenyl esters (5.15, 5.18-5.20) were synthesized according to the procedure of Trombini \textit{et al}\textsuperscript{21} or via slight modifications of that procedure. Condensation of the corresponding acid bromide and aldehyde gave pure trans-isomers after crystallisation from \textit{n}-pentane or \textit{n}-pentane/EtOAc mixtures, except for 5.18. This compound was isolated as a mixture of the 2 isomers (1:4 \textit{E}/\textit{Z} ratio, \textsuperscript{1}H NMR) that could not be separated by conventional techniques such as
chromatography or distillation. $E/Z$ isomerization mediated by Grubbs II catalyst, I$_2$ or AgNO$_3$/SiO$_2$ did not provide pure $E$-isomer.

![Scheme 6: Synthesis of 3-bromopropenyl esters.](image)

Acid chlorides (5.21, Scheme 7) cannot be used in this reaction because (besides $E/Z$ isomers) also the product of 1,2-addition of chloride on the intermediate oxonium species is obtained (5.23, Scheme 7). The desired primary chloride could not be separated from the secondary chloride by distillation. Besides changing the leaving group, the synthesis of nitrogen analogues is an attractive target also. Such a protocol would provide access to chiral allylic amines via asymmetric C-C bond formation and would complement the existing asymmetric synthesis of chiral allylic amines by asymmetric C-N bond formation. Unfortunately, attempts to synthesize nitrogen analogues 5.25 and 5.27 were not successful. Treatment of the alkene moiety of compound 5.24 (Scheme 7) with: NBS/(PhCO$_2$)$_2$, NBS/AIBN, NBS/h$_2$(250W), NBS/(PhCO$_2$)$_2$/h$_2$(250W), SeO$_2$/H$_2$O did not yield the desired products either. Bromination of the terminal olefin of 5.24 with aq. Br$_2$ was successful, yet sequential elimination to form the internal double bond failed. Cross metathesis of 5.24 with 1,4-dibromobutane catalysed by either Hoveyda-Grubbs 2nd generation (HG II) or Grubbs II catalyst failed in both cases. Cross metathesis of 5.26 (Scheme 7) with 1,4-dibromobutane catalysed by either HG$^{10}$ or Grubbs I catalyst$^{25}$ did not provide the desired allylic bromide either. The difficulty of synthesizing these nitrogen analogues may be due to the presence of the lone pair electrons of nitrogen rendering intermediate or target molecules unstable.
5.4 Cu-catalysed h-AAA with Grignard reagents on 3-bromopropenyl esters

When E-5.15 was submitted to optimized AAA conditions\textsuperscript{18}, MeMgBr (1.15 equiv, ca. 3M in ether), (R\textsubscript{fc},R\textsubscript{fc})-(+)-TaniaPhos L13 (6 mol %), and CuBr•Me\textsubscript{2}S (5 mol %), (S)-5.16 was obtained in 85\% yield and 96\% ee (Table 1, entry 1). Furthermore, linear product 5.17 could not be detected by \textsuperscript{1}H NMR spectroscopy (<1\% by HPLC analysis). The use of (R\textsubscript{fc},S\textsubscript{fc})-(-)-JosiPhos L12 instead of ligand L13 (Entry 2) gave 75\% yield of regioisomers 5.16 and 5.17 (ratio 92:8) while 5.16 had significantly lower (80\%) ee.

\textbf{Table 1: Cu-catalysed h-AAA with Grignard nucleophiles.}

<table>
<thead>
<tr>
<th>entry</th>
<th>L</th>
<th>T(\textdegree C)</th>
<th>γ:α\textsuperscript{a}</th>
<th>yield(%)\textsuperscript{b}</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+)-L13</td>
<td>-68</td>
<td>99:1</td>
<td>85</td>
<td>(+)96</td>
</tr>
<tr>
<td>2</td>
<td>(-)-L12</td>
<td>-75</td>
<td>92:8</td>
<td>75</td>
<td>(+)80</td>
</tr>
<tr>
<td>3\textsuperscript{c}</td>
<td>(+)-L13</td>
<td>-73</td>
<td>8:92</td>
<td>36\textsuperscript{d}</td>
<td>nd</td>
</tr>
<tr>
<td>4\textsuperscript{e}</td>
<td>(+)-L13</td>
<td>-74</td>
<td>99:1</td>
<td>85</td>
<td>(+)98</td>
</tr>
<tr>
<td>5\textsuperscript{e}</td>
<td>(+)-L13</td>
<td>-74</td>
<td>99:1</td>
<td>83</td>
<td>(+)96</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Regioselectivity determined by HPLC or \textsuperscript{1}H NMR spectroscopy. \textsuperscript{b} Isolated yield. \textsuperscript{c} t-BuOMe as solvent. \textsuperscript{d} Conversion determined by \textsuperscript{1}H NMR spectroscopy. \textsuperscript{e} MeMgBr (2 equiv). \textsuperscript{f} 0.8 mol\% catalyst; nd = not determined.

Previous studies on Cu-catalysed asymmetric Grignard addition reactions\textsuperscript{3-5}, illustrate that t-BuOMe may often be used in place of CH\textsubscript{2}Cl\textsubscript{2} with no adverse effect on yield or ee. The use of t-BuOMe in the h-AAA of 5.15 led to regioisomer 5.17 with a relatively low reaction rate (Entry 3, 36\%, 12 h). To investigate the influence of the concentration of the Grignard reagent we performed a reaction...
using 2 equiv of MeMgBr. The reaction gave the desired γ-substituted product in equally good yields and regioselectivity and even a higher ee (Entry 4, 98%). Catalyst loading as low as 0.8 mol% is tolerated albeit with a slightly lower yield (83%) of the reaction still providing products with 96% ee (Entry 5).

**5.4.1 Temperature profile of the Cu-catalysed h-AAA reaction**

To investigate the influence of the temperature on the product formation, the reaction was conducted over a range of temperatures (−15 °C to −85 °C). The ester moiety displayed unexpected stability in the presence of excess Grignard reagent (2 equiv) at −15 °C. Furthermore, the regioselectivity was completely preserved and only a small drop in ee was observed (Table 2, 90%, Entry 1).

Table 2: Temperature profile of the Cu-catalysed h-AAA with Grignard nucleophiles.

<table>
<thead>
<tr>
<th>entry</th>
<th>L</th>
<th>T(°C)</th>
<th>γ:α</th>
<th>yield(%)</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+)-L13</td>
<td>−15</td>
<td>99:1</td>
<td>76</td>
<td>(+)-90</td>
</tr>
<tr>
<td>2</td>
<td>(+)-L13</td>
<td>−60</td>
<td>99:1</td>
<td>77</td>
<td>(+)-94</td>
</tr>
<tr>
<td>3</td>
<td>(−)-L13</td>
<td>−80</td>
<td>99:1</td>
<td>78</td>
<td>(−)-96</td>
</tr>
<tr>
<td>4</td>
<td>(−)-L13</td>
<td>−82</td>
<td>79:21</td>
<td>67</td>
<td>(−)-94</td>
</tr>
<tr>
<td>5</td>
<td>(+)-L13</td>
<td>−85</td>
<td>37:63</td>
<td>76</td>
<td>nd</td>
</tr>
<tr>
<td>6c</td>
<td>(+)-L13</td>
<td>−74</td>
<td>n.a.</td>
<td>&lt;5d</td>
<td>nd</td>
</tr>
</tbody>
</table>

* Regioselectivity determined by HPLC or 1H NMR spectroscopy. b Isolated yield. c Reaction without copper. d Not isolated; nd = not determined.

At −60 °C and −80 °C the ee is comparable to those obtained at −74 °C (Entry 2 and 3). Note that the opposite enantiomer of the catalyst was used at −80 °C (Entry 3) with identical results. However, at temperatures lower than −80 °C an intriguing reversal of regioselectivity was observed leading to the formation of the undesired SN2 adduct. More prominent, reversal of regioselectivity is observed at −85 °C (entries 4 and 5). These observations raised the question whether the formation of both 5.16 and 5.17 are Cu-catalysed. A control experiment in the absence of copper proved that both 5.16 and 5.17 are the result of Cu-catalysed substitution since 5.16 nor 5.17 were formed in detectable (1H NMR spectroscopy) amounts even during prolonged reaction times (entry 6, 2 d). Just a small amount of degradation of the starting material was observed.
5.4.2 Variation of the ester moiety and Grignard reagents

To investigate the steric influence of the ester group, compounds 5.18 and 5.19 and were examined (Table 3, entries 1 and 2). The sterically less demanding acetyl ester compound 5.18 (1:4 ratio E/Z) was treated with 0.3 equiv MeMgBr in the presence of CuBr/TaniaPhos-complex (5 mol%). It was observed that the E-isomer reacted faster than the Z-isomer changing the Z/E ratio from 1:4 to 1:1 (1H NMR spectroscopy). Although starting material was consumed, no identifiable formation of product was observed. The conversion of starting material to co-products may be due to the presence of relatively acidic protons of the acetoxy group which can give rise to elimination pathways.

Table 3: Use of different ester groups and Grignard reagents in the h-AAA reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R'</th>
<th>α</th>
<th>yield(%)a</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me(5.18)</td>
<td>Me</td>
<td>5.28</td>
<td>97</td>
<td>(+)96</td>
</tr>
<tr>
<td>2</td>
<td>Mes(5.19)</td>
<td>Me</td>
<td>5.29</td>
<td>97</td>
<td>(+)98</td>
</tr>
<tr>
<td>3b</td>
<td>Ph(5.15)</td>
<td>C2H5</td>
<td>5.30</td>
<td>87</td>
<td>(+)98</td>
</tr>
<tr>
<td>4c</td>
<td>Ph(5.15)</td>
<td>C4H7</td>
<td>5.31</td>
<td>99</td>
<td>(−)97</td>
</tr>
<tr>
<td>5</td>
<td>Ph(5.15)</td>
<td>C18H37</td>
<td>5.32</td>
<td>93</td>
<td>(+)96</td>
</tr>
<tr>
<td>6</td>
<td>Ph(5.15)</td>
<td>C8H9</td>
<td>5.33</td>
<td>96</td>
<td>(+)97</td>
</tr>
<tr>
<td>7</td>
<td>Ph(5.15)</td>
<td>C18H37</td>
<td>5.34</td>
<td>93</td>
<td>(+)93</td>
</tr>
<tr>
<td>8</td>
<td>Ph(5.15)</td>
<td>i-bu</td>
<td>5.35</td>
<td>93</td>
<td>(+)93</td>
</tr>
<tr>
<td>9</td>
<td>Ph(5.15)</td>
<td>C3H5</td>
<td>5.36</td>
<td>93</td>
<td>(+)93</td>
</tr>
</tbody>
</table>

a Isolated yields. b Trace amount of regioisomer was detected by 1H NMR spectroscopy. c Ligand used: (R, S)-(−)-TaniaPhos. d Based on optical rotation of the corresponding alcohol. e Ee determination by 1H and 19F NMR spectroscopic analysis of the Mosher ester of the alcohol derived from 5.32.
The more bulky mesityl ester 5.19 reacted smoothly when treated with MeMgBr in the presence of the Cu-catalyst, providing the desired branched product 5.29 in excellent yield, complete regioselectivity and high ee (entry 2).

To explore the scope of the reaction a variety of Grignard reagents containing simple alkyl moieties, long alkyl chains and functional groups that allow further manipulation were tested (entries 3-9). Simple primary saturated Grignard reagents afforded allylic esters 5.30 and 5.31 in excellent yields and high enantioselectivity (entries 3 and 4). The formation of a long-chain allylic ester 5.32 was readily achieved (entry 5). Functionalized Grignard reagents were also successfully used in the $h$-AAA reaction (entries 6 and 7). Treatment with $i$-BuMgBr or allyl-MgBr did not afford the desired $S_N2'$-product (entries 8 and 9). These results are consistent with previous experiences using this particular catalyst in combination with bulky or sp$^3$ hybridized Grignard reagents.3-5

To assess the selectivity of the Cu-catalysed $h$-AAA reaction, substrates containing potentially competitive functional groups were tested. Cinnamyl derivative 5.20 contains $\alpha,\beta$-unsaturated ester, enol ester, and allyl bromide moieties and can among others, undergo 1,4-addition, 1,2-addition, $S_N2'$- and $S_N2$-substitution (Scheme 8). The product of this substrate is particularly valuable since it presents a convenient and rapid synthesis route towards a new and versatile class of enantiomerically enriched chemical intermediates. These compounds can function, among others, as starting materials for tandem consecutive 1,4-addition-I.C. rearrangement reactions yielding 1,2-dialkyl arrays 5.39 (chapter 3) and ring closing metathesis (RCM) reactions that give access to optically active $\gamma$-butenolides 5.40 (Scheme 8). The latter transformation will not be discussed here but is subject of chapter 6.
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excellent regio- and enantioselectivity (Scheme 8, yield 80%, γ:α > 98:2, 98% ee). The synthesis of 5.38 was also performed with 0.05 mol% catalyst loading with no detrimental effect on the selectivity although the yield was somewhat lower (~10%). These results demonstrate the impressive selectivity of this catalytic system converting 5.20 to a single enantiomer of either 5.37 or 5.38. To demonstrate the synthetic applicability of the h-AAA reaction, (−)-(S)-carbocycle 5.41 was synthesized. This particular molecule has found extensive use as a chiral intermediate in complex molecule synthesis (Scheme 9).26

![Scheme 9: Synthesis of (−)-(S)-carbocycle 5.41](image)

5.5 Cu-catalysed h-AAA reactions on substituted 3-bromopropenyl esters with Grignard reagents

In an effort to expand the scope of the reaction we turned our attention to α-, β- and γ-substituted substrates 5.42-5.44 (Scheme 10).27 The use of γ-substituted-3-bromopropenyl esters 5.42 in the h-AAA reaction would lead to the formation of chiral tertiary allylic alcohols.

![Scheme 10: Substitution patterns on 3-bromopropenyl esters.](image)

β-Substituted allyl bromide 5.43 leads to products that cannot be obtained by manipulation of the terminal double bond formed during h-AAA reactions when R = alkyl. β-Substitution with a halide (5.43, R = Cl, Br or I) would give the opportunity to perform transition-metal mediated coupling reactions like e.g. the Heck28 and the Suzuki coupling29. γ-Substituted substrate 5.44 is interesting from a mechanistical point of view because the substrate itself is chiral. Furthermore these chiral substrates might provide a route optically active allyl bromides through kinetic resolution protocols.

5.5.1 Synthesis of α-, β- and γ-substituted 3-bromopropenyl esters

For the synthesis of α-, β- and γ-substituted 3-bromopropenyl esters a method analogous to the synthesis of substrates 5.15, 5.18-5.20 was used.21 When methyl vinyl ketone 5.46 was stirred with benzyol bromide 5.45 in CH2Cl2 at room
temperature, no formation of product occurred even upon stirring for 4 d (Table 4, entry 1). When methacrolein 5.47 reacted with 5.45 in CH₂Cl₂ upon heating to reflux for 15 h, \( E \)-5.53 was obtained as white crystals (31%) after crystallization from \( n \)-pentane (entry 2).

**Table 4: Synthesis of \( \alpha \)-, \( \beta \)- and \( \gamma \)-substituted 3-bromopropenyl esters.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R )</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (5.46)</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>– (5.52)</td>
</tr>
<tr>
<td>2 (5.47)</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>31 (5.53)</td>
</tr>
<tr>
<td>3 (5.48)</td>
<td>H</td>
<td>Br</td>
<td>H</td>
<td>45 (5.54)</td>
</tr>
</tbody>
</table>

2-Bromo-acrolein 5.48 was synthesized via straightforward bromination of acrolein with \( \text{Br}_2 \) and sequential elimination with \( \text{Et}_3\text{N} \). When reacted with 5.45 it provided product Z-5.54 in moderate yield after crystallization from \( n \)-pentane (entry 3, 45%). \( \alpha \)-Substitution with alkyl groups (entry 4, 5 and 6) proved to be more challenging. The compounds were unstable at room temperature. These secondary bromides are more susceptible to spontaneous elimination and are thus difficult to purify. Only 5.55 \( R^2 = \text{Me} \) could be isolated by crystallization from \( n \)-pentane (–50 °C) although some impurities remained present (1H NMR spectroscopy) that could not be removed through repeated crystallization.

### 5.5.2 Cu-catalysed \( h \)-AAA reactions on \( \beta \)-methyl 3-bromopropenyl esters with ferrocenyl ligands and Grignard reagents

Reaction of substrate 5.53 with MeMgBr in the presence of a catalytic amount (5 mol%) of CuBr•SMe₂ and L13 was ineffective, returning starting material only (Table 5, entry 1). The more reactive EtMgBr provided the desired product, albeit favouring the undesired \( \alpha \)-regioisomer 5.59. Moreover, the reaction was rather slow, reaching only 50% conversion overnight (entry 2). Increasing the amount of catalyst (10 mol%) and prolonged reaction times (3 d) raised the conversion upto 80% but resulted in the formation of more co-products also. The regioselectivity decreased and enantioselectivity toward the desired \( \beta \)-product was low (entry 3, ee = 5%).
Table 5: h-AAA on β-methyl 3-bromopropenyl esters using ferrocenyl based ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>[CuX]</th>
<th>L</th>
<th>convn(%)</th>
<th>γ:α</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>CuBr•SMe₂</td>
<td>L13</td>
<td>0</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>2ᵇ</td>
<td>Et</td>
<td>CuBr•SMe₂</td>
<td>L13</td>
<td>50</td>
<td>1:5</td>
<td>nd</td>
</tr>
<tr>
<td>3ᶜ</td>
<td>Et</td>
<td>CuBr•SMe₂</td>
<td>L13</td>
<td>80</td>
<td>1:7</td>
<td>5</td>
</tr>
<tr>
<td>4ᵉ</td>
<td>Et</td>
<td>CuBr•SMe₂</td>
<td>L13</td>
<td>Many side products, s.m.</td>
<td>1:2</td>
<td>nd</td>
</tr>
<tr>
<td>5ᵍ</td>
<td>Et</td>
<td>CuBr•SMe₂</td>
<td>L13</td>
<td>Trace of α and β product, degradation</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>6ʰ</td>
<td>Et</td>
<td>CuBr•SMe₂</td>
<td>L13</td>
<td>Trace of α and β product, degradation</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>Et</td>
<td>CuTC</td>
<td>L13</td>
<td>Trace of α and β product, degradation</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>CuBr•SMe₂</td>
<td>L14</td>
<td>46% yield</td>
<td>1:3</td>
<td>nd</td>
</tr>
</tbody>
</table>

ⁿ Reaction conditions: 5 mol% cat, 2 equiv Grignard reagent, T = −75 °C, t = ~14 h, unless noted otherwise, s.m. = starting material; nd = not determined. b Determined by ¹H NMR spectroscopy. c Remaining starting material. d t = 3 d. e 10 mol% CuL13. f T = 0 °C. g Slow addition of EtMgBr, h Solvent: t-BuOMe, i Solvent: CDCl₃.

Slow addition of EtMgBr to 5.53 at 0 °C proceeded faster and the regioselectivity was slightly better (entry 4, 1:2) yet multiple co-products dominated the reaction mixture. Since solvents have a large influence on the regioselectivity of the h-AAA reaction, t-BuOMe and CDCl₃ were tested as an alternative solvent. The use of t-BuOMe gave starting material only and CDCl₃ resulted predominantly in degradation of starting material (entries 5 and 6). The use of CuTC as the copper source did not provide the desired product (entry 7). When reverse JosiPhos L14 was used as the ligand, products were obtained albeit in moderate yield and with the regioselectivity in favour of the undesired Sₐ₂-regioisomer (entry 8). These observations, in combination with results from similar catalyst systems in 1,4-addition reactions³⁻⁵ indicate that these ferrocenyl based catalysts do not tolerate sterically demanding nucleophiles or electrophiles. To overcome these limitations sterically less hindered ligands were investigated.

5.5.3 Cu-catalysed h-AAA reactions on β-substituted 3-bromopropenyl esters with phosphoramidite ligands and Grignard reagents

In the hope to successfully perform a h-AAA reaction on β-substituted substrates and overcome the limitations imposed by the use of ferrocenyl ligands L13 and L14, we turned our attention to another class of ligands. Phosphoramidites L1-L4 are sterically less hindered ligands then ferrocenyl ligands and are known to promote asymmetric allylic alkylations on β-substituted substrates (Table 1).³¹
When phosphoramidite (3.3 mol%) \( \text{L1} \) was used in combination with CuTC (3 mol%) and EtMgBr (1.15 equiv) the desired product was obtained in moderate yield, good enantioselectivity and significantly higher regioselectivity (Table 6, entry 1) than reactions using ferrocenyl ligands (vide infra 5.5.2). Comparable results were achieved upon changing the copper source from CuTC to CuBr•SMe₂ (entry 2).

Table 6: h-AAA on \( \beta \)-methyl 3-bromopropenyl esters with phosphoramidite ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>yield(%) a</th>
<th>( \gamma:\alpha )</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>L1</td>
<td>48(70)</td>
<td>2:1</td>
<td>80</td>
</tr>
<tr>
<td>2c</td>
<td>L1</td>
<td>56</td>
<td>1:1</td>
<td>75</td>
</tr>
<tr>
<td>3d</td>
<td>L1</td>
<td>97</td>
<td>2.5:1</td>
<td>97</td>
</tr>
<tr>
<td>4e</td>
<td>L1</td>
<td>96</td>
<td>2:1</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>L24</td>
<td>71</td>
<td>21:1</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>L25</td>
<td>(70)</td>
<td>1:2</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>L4</td>
<td>80</td>
<td>2:1</td>
<td>rac</td>
</tr>
</tbody>
</table>

* Reaction conditions: \( t = \sim 14 \) h, unless noted otherwise, nd = not determined, Rac = racemic. a Conversion by \( ^1\)H NMR spectroscopy between parenthesis b \( t = 3 \) h • CuBr•SMe₂ c Slow addition (over 1 h) of EtMgBr d Slow (over 1 h) addition of \( n \)-pentylMgBr (5.60b and 561b).

Elongated reaction times (reaction overnight \( \sim 14 \) h) and slow addition of the Grignard reagent, presumably preventing the formation of higher order cuprates\(^32\), provided products in excellent yield and ee, however, only modest regioselectivities, (2.5:1 and 2:1, respectively) were obtained (entries 3 and 4). Preliminary results from a survey of a small number of different phosphoramidite ligands \( \text{L24}, \text{L25} \) and \( \text{L4} \) revealed that excellent regioselectivities (entry 5, 21:1), can be achieved using phosphoramidites as ligands, albeit with low enantioselectivities (entries 5, 6 and 7). Submitting dibromide 5.44 to h-AAA reaction conditions using either CuBr•SMe₂/\( \text{L13} \) or CuTC/\( \text{L1} \) complexes and EtMgBr in CH₂Cl₂ did not provide the desired product; in both cases degradation of starting material was observed.
5.6 Cu-catalysed h-AAA reactions of 3-bromopropenyl esters with sterically hindered Grignard reagents and NHC and Binap ligands

CuBr•SMe2/L13 complexes as catalysts for the h-AAA reaction do not promote (vide infra) the selective addition of sterically hindered Grignard reagents. N-Heterocyclic carbene33 (NHC) ligand L26 on the other hand promotes selective 1,4-addition of sterically hindered Grignard reagents with high selectivity on β-substituted substrates, forming enantioenriched all carbon quaternary centres (Scheme 12).34

Scheme 12: 1,4-Addition of sterically hindered Grignard reagents by Cu/L26 complexes.

Loh et al recently reported the complex of (R)-Tol-BINAP L15 and Cul as a selective catalyst for 1,4-additions of Grignard reagents to α,β-unsaturated esters35. Besides linear Grignard reagents the catalyst also allowed the selective addition of sterically hindered Grignard reagents (Scheme 13). In comparison, catalysts based on ferrocenyl ligands (vide infra) give poor results for those type of additions.
Both ligands L26 and L15 display a higher tolerance toward sterically demanding Grignard reagents. Ligand L26 (4 mol%), synthesized via a slight modification of the procedure reported by Alexakis et al, was used in the h-AAA reaction of 5.15 with Cu(OTf)2 (3 mol%) and i-BuMgBr. The reaction was relatively slow, reaching 40% conversion in 25 h with no preference for either one of the two regioisomers (Table 7, entry 1). Moreover, 1H NMR spectroscopic analysis of the crude reaction mixture indicated the presence of a number of unidentified co-products. To investigate the catalytic properties of the complex of Cu(OTf)2 and L26 when using β-substituted (R = Me) substrates, 5.53 was reacted with EtMgBr in CH2Cl2 in the presence of Cu/L26 complex. In this case, 1H NMR spectroscopic analysis of the crude reaction mixture showed a clean and complete conversion toward the undesired SN2-regioisomer 5.72.

Table 7: h-AAA on 3-bromopropenyl esters with Tol-BINAP and NHC ligands.

<table>
<thead>
<tr>
<th>entry</th>
<th>Solvent</th>
<th>[CuX]</th>
<th>L</th>
<th>R</th>
<th>R'MeBr</th>
<th>t(h)</th>
<th>convn(%)a</th>
<th>γ:αa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>Et2O</td>
<td>Cu(OTf)2</td>
<td>L26</td>
<td>H</td>
<td>i-Bu</td>
<td>24</td>
<td>40</td>
<td>1:1</td>
</tr>
<tr>
<td>2b</td>
<td>CH2Cl2</td>
<td>Cu(OTf)2</td>
<td>L26</td>
<td>Me</td>
<td>Et</td>
<td>18</td>
<td>100</td>
<td>0:1</td>
</tr>
<tr>
<td>3c</td>
<td>CH2Cl2</td>
<td>Cul</td>
<td>L15</td>
<td>H</td>
<td>c-Pentyl</td>
<td>8</td>
<td>100</td>
<td>1.5:1</td>
</tr>
<tr>
<td>4c</td>
<td>t-BuOMe</td>
<td>Cul</td>
<td>L15</td>
<td>H</td>
<td>c-Pentyl</td>
<td>8</td>
<td>100</td>
<td>nd</td>
</tr>
</tbody>
</table>

*Conversion and regioselectivity determined by 1H NMR spectroscopy. * Reaction conditions: 3 mol% Cu(OTf)2, 4 mol% L26, 1.2 equiv i-BuMgBr or EtMgBr, T = −58 °C. * Reaction conditions: 5 mol% Cu(OTf)2, 7.5 mol% L15, 3 equiv c-pentylMgBr, T = −44 °C.

Using the complex derived from Cul and L15 in combination with c-pentylMgBr and 5.15 in CH2Cl2 provided products 5.71 and 5.72 with better regioselectivity (Entry 3, 1.5:1). Unfortunately, 1H NMR spectroscopic analysis of the crude mixture revealed that the reaction outcome was dominated by the formation of co-
products that were not further identified. Performing the same reaction in t-BuOMe gave degradation of starting material 5.15 only (Entry 4).

### 5.7 Iterative (hetero)-allylic asymmetric alkylation

To augment the synthetic relevance of the ACA and the AAA reaction, a program was started to investigate the exploitation of the functional groups, the ester and olefin moiety present after the ACA- and AAA-reaction, respectively. Firstly a strategy was developed that exploits the olefin moiety created in the AAA and combines the AAA with the ACA into the synthesis of syn- and anti-1,2-dialkyl esters (Scheme 14, 5.75 and 5.76). Thus when the conversion of 5.73 using standard AAA conditions and MeMgBr was followed by cross metathesis with methyl acrylate using HGII (2 mol%), intermediate 5.74 was obtained in moderate yield (66%). Subsequently the acquired α,β-unsaturated ester 5.74 was converted to the desired syn-5.75- or anti-5.76-1,2-dialkyl ester with EtMgBr in the presence of CuBr•SMe₂/L12 depending on the configuration of the ligand used (Scheme 14). The configuration of the second stereogenic centre is entirely ligand controlled. A control experiment performed without chiral ligand showed a strong bias for the anti-product 5.75 (86:14).

**Scheme 14: AAA followed by 1,4-addition.**

A second strategy developed in our group is the iterative 1,4-addition on α,β-unsaturated thioesters. For example, the CuBr/L12 catalysed addition of MeMgBr to compound 5.77 gave chiral intermediate 5.78 in excellent yield and ee. Sequential reduction with DIBAL-H to the aldehyde followed by Wittig olefination gave α,β-unsaturated thioester 5.79 and set the stage for the next 1,4-addition. Repeating this sequence a number of times to build up the 1,3-oligomethyl...
(deoxypropionate) array comprised the iterative synthesis of phthioceranic acid (a constituent of the virulence factor Sulfolipid-I, *Mycobacterium tuberculosis*) 5.81, in a short, practical and robust approach (Scheme 15). \(^{37}\)

**Scheme 15: The iterative 1,4-addition**

In analogy to above mentioned strategies a logical and useful extension of the h-AAA and the AAA reaction would be to develop iterative protocols building chiral 1,2-alkyl arrays (Scheme 16). In contrast to 1,3-alkyl arrays, (deoxypropionate units) which are abundantly present in nature\(^{38}\), 1,2-alkyl arrays are not profusely represented. Even though 1,2-alkyl architectures may not be that interesting for complex molecule synthesis, they may find application in a number of related areas eg: artificial chiral lipids\(^{39}\), well defined chiral oligobutylene\(^{40}\). A synthesis strategy based on (h)-AAA reactions to synthesise oligo-1,2-alkyl arrays starts with the (h)-AAA (depending on the nature of the R group) of compound 5.15 to give chiral intermediate 5.82. Cross metathesis (CM) of the terminal olefin with an appropriate allyl bromide creates allyl bromide 5.83 that can undergo an AAA reaction. Repeating steps A and B builds up the oligo-1,2-alkyl architectures 5.84 or 5.85 in short and convenient manner (Scheme 16).

**Scheme 16: Iterative (h)-AAA strategy and possible applications.**
5.7.1 Synthesis of oligo-1,2-alkyl architectures

When compound 5.16 was reacted with 1,4-dibromo-2-butene in the presence of a catalytic amount of HG II at reflux in CH₂Cl₂ for 25 h, allylic bromide (E)-5.86 was obtained in good yield (77%, Scheme 17). Formation of the (Z)-isomer was not observed (¹H NMR spectroscopy). Attempts to synthesize 5.86 via reaction of 5.16 with allyl bromide (4 equiv) in the presence of HG II (5 mol%) in CH₂Cl₂ at reflux (5 d) failed and only unreacted starting material was obtained. When Grubbs I (5 mol%) catalyst was used in combination with 5.16 and 1,4-dibromo-2-butene (10 equiv) in CH₂Cl₂ no reaction occurred even after 5 d at reflux.

![Scheme 17: The iterative h-AAA strategy, synthesis of 1,2-dialkyl arrays.](image)

The next step en route to an iterative synthesis of oligo-1,2-dialkyl architectures is the AAA of 5.86. Using optimized AAA conditions, 5.87 reacted smoothly with MeMgBr at −74 °C in the presence of Cu/L13 (5 mol%) and gave full conversion in a clean reaction to the undesired α-regioisomer 5.88. Increasing the catalyst loading upto 10 mol% did not influence the regioselectivity. The secondary chiral ester moiety may be too bulky for this catalyst, pushing the system toward α-substitution. Further research on this topic was discontinued in view of time limits.
5.8 Conclusions and outlook

The $h$-AAA (hetoro-allylic asymmetric alkylation) reaction was developed and a short and practical synthesis toward optically enriched low molecular weight protected allylic alcohols was obtained. The $h$-AAA reaction with the complex of CuBr•SMe$_2$ and chiral ligand L13 (TaniaPhos), provides protected allylic alcohols in high yield (up to 99%) and with excellent selectivities (complete regioselectivity and up to 98% ee). β-Substituted substrates could not be selectively alkylated, using CuBr•SMe$_2$ and ligand L13. However, the complex of CuTC and phosphoramidite L1 catalysed the $h$-AAA to β-substituted substrates and the γ-substituted products were obtained with high yields, moderate regioselectivity and excellent enantioselectivity (97%, 2.5:1 and 98%, respectively). A short screening of a small number of phosphoramidite ligands showed that high regioselectivities (21:1) can be achieved, although in those cases the ee remained low. A high throughput screening of large a number of phosphoramidite ligands should allow the successful identification of the optimal ligand for this transformation. Current limitations of the $h$-AAA reaction are substitution with sp$^2$ hybridized, sp$^3$ hybridized secondary and sterically demanding Grignard reagents. Preliminary experiments with copper complexes of NHC L26 or (Tol)$_2$Binap L15 showed that substitution with bulky Grignard reagents is possible in the $h$-AAA reaction. However these procedures need further optimization to reach acceptable levels of selectivity. The first step (cross metathesis) toward an iterative ($li$)-AAA protocol directed at the synthesis of oligo-1,2-dialkyl architectures was taken but the second step (AAA) has not been established and requires more research.
5.9 Experimental section

For general remarks see, Chapter 2.

Ligands:
L1, L2, L3, L4 were synthesized according to literature procedures or slight modification of literature procedures (L2, Lit: precipitation of product from the water layer. Modification: extraction of the H2O layer with CH2Cl2 provided pure product).

Grignard reagents:
The following Grignard reagents were purchased from Aldrich as solutions in Et2O: MeMgBr (3M), EtMgBr (3M), i-BuMgBr (2M), PentMgBr (2M), allylMgBr (1M). Other Grignard reagents were prepared from the corresponding alkyl bromides and magnesium turnings in Et2O following standard procedures.

Synthesis of starting materials:
All starting materials were synthesized according to literature procedures or modified procedures, and Analytical data are reported for compounds 5.19, 5.20, 5.53 and 5.54. Benzoyl bromide and acetyl bromide were purchased from Aldrich.

(E)-3-bromopropenyl 2,4,6-methyl benzoate (5.19)
Compound 5.19 was synthesized according to literature procedure. Recrystallization from n-pentane gave 5.19 (212 mg, 12%) as white crystals: Mp.: 74–96 °C; 1H NMR (CDCl3, 400 MHz) δ 7.69 (d, J = 12.4 Hz, 1 H), δ 6.89 (s, 1 H), 5.80 (td, J = 12.3, 8.4 Hz, 1H), 4.05 (d, J = 8.4 Hz, 2H), δ 2.33 (s, 6 H), δ 2.30 (s, 3 H); 13C NMR (CDCl3, 100.6 MHz) δ 166.1 (s), 140.3 (s), 139.1 (d), 136.1 (s, 2 x C), 128.6 (d, 2 x C), 128.5 (s), 111.7 (d), 28.4 (t), 21.1 (q), 20.0 (q, 2 x C); LRMS (EI) m/z: 284 (M+), 164, 147 (100), 119, 91.

(E)-3-bromopropenyl cinnamate (5.20)
Compound 5.20 was synthesized according to literature procedure. Recrystallization from n-pentane/EtOAc mixtures gave 5.20 as white needles: Mp.: 94–95 °C; 1H NMR (CDCl3, 400 MHz) δ 7.81 (d, J = 16.0 Hz, 1 H), 7.41–7.53 (m, 3 H), 7.44–7.38 (m, 3 H) 6.45 (d, J = 16.0 Hz, 1 H), 5.80 (td, J = 12.4, 8.4 Hz, 1H), 4.04 (d, J = 8.4 Hz, 2H); 13C NMR (CDCl3, 100.6 MHz) δ 163.6, 147.6, 139.6, 134.2, 131.2 (2 x C), 129.2 (2 x C), 128.6, 116.3, 111.6, 29.0; exact mass m/z calcd for C13H11O2Br 267.9942, found 267.9929.
**(E)-3-bromo-β-methyl-propenyl benzoate (5.53)**

Methacrolein (0.45 ml, 5.4 mmol) was added to a stirred solution of benzoyl bromide (0.64 ml, 5.4 mmol) in CH₂Cl₂ at room temperature. The resulting mixture was heated to reflux for 15 h before cooling to room temperature and quenching with aq. sat. NaCO₃. The mixture was partitioned between CH₂Cl₂ and water, and the aqueous layer extracted three times with CH₂Cl₂. The organic layer was dried (MgSO₄), filtered and the solvent evaporated in vacuo yielding a yellow oil that was taken up in n-pentane. At −60 °C the product crystallized from n-pentane. Filtration gave 5.53 (400 mg, 31%) as thin white needles: Mp.: 40−42 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.14-8.05 (m, 2 H), 7.66-7.42 (m, 4 H) 4.06 (s, 2 H), 1.97 (s, 3 H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 162.8, 133.7, 133.6, 129.8 (2 x C), 128.6, 128.4 (2 x C), 118.8, 36.1, 12.9; exact mass m/z calcd for C₁₁H₁₁O₂Br 255.9922, found 255.9907. The (E)-configuration was determined by 2D-NOE-NMR spectroscopy.

**(Z)-2,3-dibromopropenyl benzoate (5.54)**

Benzoyl bromide (5.53 ml, 4.7 mmol) was added to a stirred and cooled solution at −70 °C, of α-bromo-acrolein (5.69 g, 4.7 mmol) in CH₂Cl₂ (75 ml). After 1 h the mixture was removed from the cold bath and a spatula point of ZnCl₂ (dried) was added. Stirring was continued for 1 h before cooling down to −15 °C and the mixture was kept at that temperature overnight. 5.54 crystallized as thin white needles (1.76 g) that were isolated by filtration. The mother liquor was partitioned between CH₂Cl₂ and aq. sat. NaCO₃, and the aqueous layer extracted 1x with CH₂Cl₂. The organic layer was dried (MgSO₄), filtered and the solvent evaporated in vacuo yielding an off white solid. Multiple crystallizations from Et₂O/ n-pentane (1:2) at −15 °C gave 5.54 as white crystals (4.94 g): total yield 6.70 g, 45%; Mp: 104−106(dec.); ¹H NMR (CDCl₃, 300 MHz) δ 8.20-8.05 (m, 3 H), 7.69-7.60 (m, 1 H), 7.55-7.45 (m, 2 H) 4.26 (s, 2 H); ¹³C NMR (CDCl₃, 125.7 MHz) δ 162.1 (s), 136.1 (d), 134.3 (d), 130.4 (d, 2 x C), 128.7 (d, 2 x C), 127.7 (s), 107.6 (s), 34.5 (t); exact mass m/z calcd for C₁₀H₁₁O₂Br₂ 319.8871, found 319.8885; The (Z)-configuration was determined by 2D-NOE-NMR spectroscopy.

**General procedure for the synthesis of racemic allylic esters:**

Racemic allylic esters were synthesized by modification of a literature procedure. The Grignard reagent (1.0 equiv) in Et₂O (1–3 M) was added dropwise over 5 min to a stirred and cooled (−15 °C) solution of freshly distilled acrolein (1.1 equiv) in THF. Stirring was continued for 1 h before the mixture was warmed to room temperature, quenched with water, partitioned between water and ether and the aqueous layer extracted with Et₂O. The combined organic layers were washed with brine, dried (MgSO₄), and the solvent carefully evaporated in vacuo. The crude alcohol (1 equiv) was used without further purification. Benzoyl chloride (1.1 equiv) was injected into a cooled (0 °C) solution of crude alcohol (1 equiv) and pyridine (2 equiv) in CH₂Cl₂. The reaction mixture was allowed to warm to room temperature and stirred for 1 h, before the solvent was evaporated in vacuo. The
residue was taken up in Et₂O and washed with aq. 2N KOH, aq. 1N H₂SO₄, sat. aq. NaHCO₃ and brine. The organic layer was dried (MgSO₄), and the solvent evaporated in vacuo. Flash chromatography of the residue over silica gel, using n-pentane or Et₂O/ n-pentane mixtures, gave racemic allylic esters as clear colorless oils.

**Synthesis of chiral allylic esters:**

**General procedure A**

CH₂Cl₂ was added to a mixture of CuBr•SMe₂ (5 mol%) and TaniaPhos (6 mol%) under a nitrogen atmosphere at room temperature and the orange solution was stirred for 10 min before cooling to −75 °C. While ensuring that stirring continued, the Grignard reagent (1.3 equiv in Et₂O) was added dropwise over 2 min. After an additional 15 min the allylic bromide in CH₂Cl₂ (0.7 mL) was added dropwise over 5 min. Stirring at −75 °C was continued (typically overnight) and the reaction mixture was then quenched by the addition of MeOH (ca. 1 mL). The reaction mixture was removed from the cooling bath and sat. aq. NH₄Cl (ca. 1 mL), and then water (ca. 2 mL) were added. The mixture was partitioned between Et₂O (5 mL) and water, and the aqueous layer extracted three times with Et₂O. The combined organic layers were dried (MgSO₄), filtered and the solvent evaporated in vacuo.

**General procedure B**

The Grignard reagent (1.3–2.0 equiv in Et₂O) was added dropwise over 5 min to a homogeneous, stirred and cooled (−75 °C) solution of the allylic bromide, CuBr•SMe₂ (5 mol%) and TaniaPhos (5 mol%) in CH₂Cl₂ (2.5 mL) under a nitrogen atmosphere. If the solution was not again homogeneous after 5 min, further minimal portions of CH₂Cl₂ were added to dissolve precipitates. Stirring was continued until 1H NMR or TLC (5% Et₂O/n-pentane) analysis showed the reaction had reached completion (typically overnight) and the reaction was quenched with MeOH (5 mL). The reaction mixture was removed from the cooling bath and sat. aq. NH₄Cl (ca. 5 mL) was added. The mixture was partitioned between CH₂Cl₂ (5 mL) and water. The organic layer was dried (MgSO₄), filtered and the solvent evaporated in vacuo.

(+)-(S)-Benzoic acid-1-methyl-allyl ester (5.16)⁴⁴

Methylmagnesium bromide (3.0 M, 0.50 mL, 1.5 mmol) was added dropwise over 2 min to a stirred and cooled (−73 °C) solution of 5.15 (180 mg, 0.75 mmol), CuBr•SMe₂ (8.1 mg, 39 µmol) and (R,S)-TaniaPhos (32.2 mg, 45.4 µmol) in CH₂Cl₂ (3 mL) under a nitrogen atmosphere. Stirring was continued for 18 h at −73 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using first n-pentane and then 100:1 n-pentane/Et₂O gave 5.16 (112 mg, 85%) as a clear colorless oil: [α]₂⁰⁵ = +43.7 (c 0.35, CHCl₃), Lit.: [α]₂⁰⁵ = +48.03 (EtOH); ¹H NMR (CDCl₃, 400 MHz) δ 8.11–8.03 (m, 2 H), 7.59–7.51 (m, 1 H), 7.47–7.39 (m, 2 H),
(++)-2,4,6-Trimethylbenzoic acid-1-methyl-allyl ester (5.29)

Methylmagnesium bromide (3.0 M, 0.48 mL, 1.4 mmol) was added dropwise over 3 min to a stirred and cooled (–73 °C) solution of 5.19 (204 mg, 0.722 mmol), CuBr•SMe2 (8.0 mg, 38.9 µmol) and (R,R)-TaniaPhos (30.0 mg, 43.6 µmol) in CH2Cl2 (3.5 mL) under a nitrogen atmosphere. Stirring was continued for 15 h at –73 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using 2% Et2O in n-pentane gave 5.29 (143.1 mg, 91%), as a clear colorless oil: [α]275° = +12.2 (c 0.33, CHCl3); 1H NMR (CDCl3, 400 MHz) δ 6.86 (s, 2 H), 5.96 (ddd, J = 6.2, 0.5, 17.2 Hz, 1 H), 5.65 (tt, J = 1.2, 6.4 Hz, 1 H), 5.37 (td, J = 1.3, 17.3 Hz, 1 H), 5.22 (td, J = 1.2, 10.5 Hz, 1 H), 2.31 (s, 6 H), 2.29 (s, 3 H), 1.46 (d, J = 6.5 Hz, 3 H); 13C NMR (CDCl3, 100.6 MHz) δ 169.2 (s), 139.0 (s), 137.4 (d), 134.8 (s, 2 x C), 131.1 (s), 128.2 (d, 2 x C), 116.4 (t), 71.6 (d), 21.0 (q), 19.9 (q), 19.5 (q, 2 x C); exact mass m/z calcd for C14H18O2 218.1307, found 218.1303; HPLC analysis indicated an enantiomeric excess of 98% [Chiralcel OB-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99.5:0.5; λ = 230 nm; major enantiomer (+)-5.29, tR = 8.73 min; minor enantiomer (–)-5.29, tR = 9.22 min].

(++)-Benzoic acid-1-ethyl-allyl ester (5.30)

Ethylmagnesium bromide (3.0 M, 0.50 mL, 1.5 mmol) was added dropwise over 5 min to a stirred and cooled (–79 °C) solution of 5.15 (181 mg, 0.75 mmol), CuBr•SMe2 (7.2 mg, 35 µmol) and (R,r)-TaniaPhos (30.3 mg, 44 µmol) in CH2Cl2 (3 mL) under a nitrogen atmosphere. Stirring was continued for 16 h at –79 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using first n-pentane and then 2% Et2O in n-pentane gave 5.30 (124 mg, 87 %), as a clear colorless oil: [α]275° = +43.8 (c 1.5, CHCl3); 1H NMR (CDCl3, 400 MHz) δ 8.10–8.06 (m, 2 H), 7.58–7.54 (m, 1 H), 7.47–7.41 (m, 2 H), 5.90 (ddd, J = 6.2, 10.6, 17.2 Hz, 1 H), 5.48–5.41 (m, 1 H), 5.33 (td, J = 1.3, 17.3 Hz, 1 H), 5.22 (td, J = 1.3, 10.6 Hz, 1 H), 1.87–1.72 (m, 2 H), 0.99 (t, J = 7.4 Hz, 3 H); 13C NMR (CDCl3, 100.6 MHz) δ 165.8 (s), 156.2 (d), 132.7 (d), 130.6 (s), 129.5(d, 2 x C), 128.3(d, 2 x C), 116.7 (t), 76.4 (d), 27.3 (t), 9.4 (q); exact mass m/z calcd for C12H14O2 = 190.09937, found 190.09917; HPLC analysis indicated an enantiomeric excess of 98% [Chiralcel OB-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer (+)-5.30, tR = 11.62 min; minor enantiomer (–)-5.30, tR = 13.01 min].
(-)-Benzoic acid-1-vinyl-hexyl ester (5.31)\(^{45}\)

Pentylmagnesium bromide (2.0 M, 0.76 mL, 1.5 mmol) was added dropwise over 5 min to a stirred and cooled (-75 °C) solution of 5.15 (184.3 mg, 0.765 mmol), CuBr•Smel (8.0 mg, 50 μmol) and (S(o),S)-TaniaPhos (30.0 mg, 43.6 μmol) in CH₂Cl₂ (2.5 mL) under a nitrogen atmosphere. After 5 min a further 1 mL CH₂Cl₂ was added to dissolve the resulting precipitates and stirring was continued for 66 h at -75 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using first n-pentane and then 1% Et₂O/n-pentane gave 5.31 (164.0 mg, 99%) as a clear colorless oil: [α]₂⁰ = -27.6 (c 0.47, CHCl₃); \(^{1}H\) NMR (CDCl₃, 400 MHz) δ 8.07 (apparent d, J = 8.4 Hz, 2 H), 7.59–7.51 (m, 1 H), 7.47–7.40 (m, 2 H), 5.90 (ddd, J = 6.3, 10.5, 16.9 Hz, 1 H), 5.50 (dd, J = 6.4, 12.6 Hz, 1 H), 5.33 (dd, J = 1.1, 17.2 Hz, 1 H), 5.20 (dd, J = 1.1, 10.5 Hz, 1 H), 1.88–1.62 (m, 2 H), 1.50–1.18 (m, 6 H), 0.89 (br s, 3 H); \(^{13}C\) NMR (CDCl₃, 100.6 MHz) δ 166.1 (s), 136.9 (d), 133.1 (d), 129.8 (d, 2 x C), 128.5 (d, 2 x C), 116.7 (t), 75.6 (d), 34.5 (t), 31.8 (t), 24.9 (t), 22.8 (t), 14.2 (q); exact mass m/z calcd for C₁₅H₂₀O₂ 232.14632, found 232.14714; HPLC analysis indicated an enantiomeric excess of 97% [Chiralcel OB-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99.5:0.5; λ = 230 nm; minor enantiomer (+)-5.31, tᵣ = 9.74 min; major enantiomer (-)-5.31, tᵣ = 10.92 min].

(+)-Benzoic acid-1-vinyl-nonadecyl ester (5.32)

n-Octadecane magnesium bromide (1.5M in ether, 0.98 mL, 1.5 mmol) was added at a fast dropwise rate over 1 min (to avoid solidification of the Grignard in the syringe) to a stirred and cooled (-70 °C) solution of 5.15 (177.5 mg, 0.736 mmol), CuBr•Smel (8.0 mg, 50 μmol) and (R(o),S)-TaniaPhos (30.0 mg, 43.6 μmol) in CH₂Cl₂ (2.5 mL) under a nitrogen atmosphere. After 5 min a further 1 mL of CH₂Cl₂ was added to dissolve the resulting precipitates and stirring was continued for 18 h at -70 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using first n-pentane and then 5% Et₂O/n-pentane gave impure 5.32. A solid co-product was removed by crystallization from hot diisopropyl ether (ca. 5 mL) and filtration. The mother liquor was concentrated and flash chromatography of the colorless residue over silica gel, using first n-pentane and then 2% Et₂O/n-pentane gave pure 5.32 (284.3 mg, 93%) as a clear colorless oil: [α]₂⁰ = +17.0 (c 0.094, CHCl₃); \(^{1}H\) NMR (400 MHz) δ 8.07 (apparent d, J = 8.4 Hz, 2 H), 7.58–7.52 (m, 1 H), 7.47–7.41 (m, 2 H), 5.95–5.84 (m, 1 H), 5.49 (apparent q, J = 6.5 Hz, 1 H), 5.32 (dd, J = 0.6, 17.2 Hz, 1 H), 5.20 (dd, J = 1.0, 10.5 Hz, 1 H), 1.87–1.66 (m, 2 H), 1.45–1.20 (m, 32 H), 0.88 (t, 3 H, J = 6.8 Hz); \(^{13}C\) NMR (CDCl₃, 100.6 MHz) δ 165.9 (s), 136.6 (d), 132.8 (d), 130.6 (s), 129.6 (d, 2 x C), 128.3 (d, 2 x C), 116.5 (t), 75.4 (d), 34.3 (t), 31.8 (t), 24.9 (t), 22.8 (t), 14.2 (q); exact mass m/z calcd for C₂₈H₄₆O₂ 414.34977, found 414.35186. Optical rotation was measured on the corresponding alcohol of (+)-benzoic acid-1-vinyl-nonadecyl ester:
Enantiomeric excess was measured by $^1$H NMR and $^{19}$F NMR analysis of the corresponding Mosher ester >95%.

Butenylmagnesium bromide (1.1M, 1.37 mL, 1.51 mmol) was added dropwise over 2 min to a stirred and cooled (−73 °C) solution of 5.15 (182.0 mg, 0.755 mmol), CuBr•SMe$_2$ (8.0 mg, 50 μmol) and (R,S)-TaniaPhos (30.0 mg, 43.6 μmol) in CH$_2$Cl$_2$ (3.5 mL) under a nitrogen atmosphere. Stirring was continued for 20 h at −73 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using 2% Et$_2$O/n-pentane gave 5.33 (156.3 mg, 96%) as a clear colorless oil: [α]$^{{20}}_{D}^{89} = +27.2$ (c 0.29, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.11–8.06 (m, 2 H), 7.59–7.53 (m, 1 H), 7.48–7.42 (m, 2 H), 5.87 (dddd, J = 6.4, 10.4, 13.2, 27.3 Hz, 2 H), 5.57–5.51 (m, 1 H), 5.35 (td, J = 1.3, 17.2 Hz, 1 H), 5.23 (td, J = 1.2, 10.5 Hz, 1 H), 5.05 (dd, J = 1.6, 3.4, 17.1 Hz, 1 H), 5.02–4.98 (m, 1 H), 2.20 (qdd, J = 1.4, 6.7, 13.3 Hz, 2 H), 1.98–1.88 (m, 2 H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) δ 165.6 (s), 137.4 (d), 136.2 (d), 132.7 (d), 130.3 (s), 129.4 (d, 2 x C), 128.2 (d, 2 x C), 116.7 (t), 115.1 (t), 74.5 (d), 33.3 (t), 29.2 (t); exact mass m/z calcd for C$_{14}$H$_{16}$O$_2$ 216.11502, found 216.11595; HPLC analysis indicated an enantiomeric excess of 97% [Chiralcel OB-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99.75:0.25; λ = 220 nm; major enantiomer (+)-5.33, tR = 15.82 min; minor enantiomer (−)-5.33, tR = 18.76 min]. The absolute configuration is based on the conversion to the absolute configuration of known 5.41.

Phenyl ethylmagnesium bromide (1.1M, 1.37 mL, 1.51 mmol) was added dropwise over 2 min to a stirred and cooled (−73 °C) solution of 5.15 (183.1 mg, 0.760 mmol), CuBr•SMe$_2$ (8.0 mg, 50 μmol) and (R,S)-TaniaPhos (30.0 mg, 43.6 μmol) in CH$_2$Cl$_2$ (3.5 mL) under a nitrogen atmosphere. Stirring was continued for 16 h at −73 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using first n-pentane and then 5% Et$_2$O/n-pentane gave impure 5.34. A second, more careful, round of chromatography over silica gel, using first n-pentane and then 2% Et$_2$O/n-pentane gave 5.34 (188.2 mg, 93%) which still contained a 1H NMR detectable amount of Grignard homo-coupled impurity: [α]$^{{20}}_{D}^{89} = +8.1$ (c 0.42, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.12–8.08 (m, 2 H), 7.62–7.56 (m, 1 H), 7.51–7.45 (m, 2 H), 7.34–7.28 (m, 2 H), 7.24–7.18 (m, 3 H), 5.96 (dd, J = 6.2, 10.6, 17.1 Hz, 1 H), 5.57 (dd, J = 1.1, 6.0, 12.0 Hz, 1 H), 5.39 (td, J = 1.3, 17.2 Hz, 1 H), 5.27 (td, J = 1.2, 10.6 Hz, 1 H), 2.78 (dd, J = 4.7, 6.4, 9.0 Hz, 2 H), 2.23–2.04 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) δ 166.0 (s), 141.6 (s), 136.5 (d), 133.2 (d), 130.7 (s), 129.9 (d, 2 x C), 128.7 (d, 2 x C), 128.6 (d, 4 x C), 126.3 (d), 117.3 (t), 75.0 (d), 36.2 (t), 31.7 (t); exact mass m/z calcd C$_{18}$H$_{18}$O$_2$ 266.13067, found 266.12978; HPLC analysis indicated an enantiomeric excess of 93% [Chiralcel OB-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99.75:0.25; λ = 220 nm; major enantiomer (+)-5.34, tR = 15.68 min; minor enantiomer (−)-5.34, tR = 18.76 min].
(+)-(E)-3-Phenyl-acrylic acid-1-methyl-allyl ester (5.37)

CH₂Cl₂ (1 mL) was added to a mixture of CuBr•SMe₂ (3.4 mg, 17 μmol) and (Rfe,S)-TaniaPhos (15.4 mg, 22.5 μmol) under a nitrogen atmosphere at room temperature, and the resulting orange solution was stirred for 10 min before cooling to −77 °C. While ensuring that stirring continued, MeMgBr (3M, 0.14 mL, 0.47 mmol) was added dropwise over 2 min, to provide a yellow mixture. After an additional 15 min 5.20 (100.2 mg, 0.375 mmol) in CH₂Cl₂ (0.7 mL) was added dropwise over 5 min. Stirring at −77 °C was continued for 13 h. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel using 100:1 n-pentane-Et₂O gave 5.37 (60 mg, 80%) as a clear colorless oil: [α]²⁰ós = +50.0 (c 0.04, CHCl₃); ¹H NMR (300 MHz) δ 7.70 (d, J = 16.0 Hz, 1 H), 7.52–7.46 (m, 2 H), 7.37–7.32 (m, 3 H), 6.46 (d, J = 16.0 Hz, 1 H), 5.93 (ddd, J = 5.8, 10.5, 17.2 Hz, 1 H), 5.55–5.46 (m, 1 H), 5.31 (td, J = 1.2, 17.3 Hz, 1 H), 5.18 (td, J = 1.2, 10.5 Hz, 1 H), 1.40 (d, J = 6.5 Hz, 3 H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 165.8 (s), 144.4 (d), 137.5 (d), 134.2 (s), 129.9 (d), 128.6 (d, 2 x C), 127.8 (d, 2 x C), 118.2 (d), 115.5 (t), 70.7 (d), 19.7 (q); exact mass m/z calcd for C₁₃H₁₄O₂ 202.09937, found 202.10045; HPLC analysis indicated an enantiomeric excess of 98% [Chiralcel OB-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99.5:0.5; λ = 225 nm; minor enantiomer (–)-5.37, tᵣ = 21.10 min; major enantiomer (+)-5.37, tᵣ = 22.35 min].

(+)-(S)-(E)-3-Phenyl-acrylic acid-1-ethyl-allyl ester (5.38)

Ethylmagnesium bromide (3.0 M, 2.1 mL, 6.4 mmol) was added dropwise over 5 min to a stirred and cooled (–73 °C) solution of 5.20 (852.7 mg, 3.194 mmol), CuBr•SMe₂ (4.8 mg, 23 μmol) and (Rfe,S)-TaniaPhos (17.2 mg, 25.0 μmol) in CH₂Cl₂ (7 mL) under a nitrogen atmosphere. Stirring was continued for 17 h at −73 °C. Work up according to procedure B. Careful flash chromatography of the dark orange residue over silica gel, using Et₂O/n-pentane mixtures from 2–5% Et₂O gave 5.38 (549.8 mg, 80%) as a clear colorless oil: [α]²⁰ós = +53.4 (c 0.058, CHCl₃); ¹H NMR (400 MHz) δ 7.71 (d, J = 16.0 Hz, 1 H), 7.55–7.51 (m, 2 H), 7.40–7.36 (m, 3 H), 6.47 (d, J = 16.0 Hz, 1 H), 5.85 (ddd, J = 6.3, 10.5, 17.0 Hz, 1 H), 5.36–5.27 (m, 2 H), 5.21 (td, J = 1.2, 10.6 Hz, 1 H), 1.82–1.65 (m, 2 H), 0.96 (t, J = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 166.2 (s), 144.6 (d), 136.3(d), 134.4(s), 130.2 (d), 128.8 (d, 2 x C), 127.9 (d, 2 x C), 118.3 (d), 116.7 (t), 76.0 (d), 27.3 (t), 9.4 (q); exact mass m/z calcd for C₁₄H₁₆O₂ 216.11502, found 216.11604; HPLC analysis indicated an enantiomeric excess of at least 98% [Chiralcel OB-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99.5:0.5; λ = 225 nm; major enantiomer (+)-5.38, tᵣ = 16.83 min; minor enantiomer, racemate, (–)-5.38, tᵣ = 17.8 min]. The absolute configuration assigned by comparison of optical rotation of the corresponding ethyl furanone see chapter 6.48.
Grubbs II catalyst (19.6 mg, 0.0231 mmol) was tipped into a stirred solution of 5.33 (97.1 mg, 0.450 mmol) in degassed CH$_2$Cl$_2$ (10 mL) under a nitrogen atmosphere. The reaction flask was placed in a preheated oil bath (60° C) and stirred while heating to reflux for 18 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. Flash chromatography of the residue over silica gel, using a 2% Et$_2$O/n-pentane mixture gave 5.41 (72.0 mg, 85%) as a clear colorless oil: $\alpha$ -285 $=\!$ -195.7 (c 0.19, CHCl$_3$), lit\textsuperscript{26}: $\alpha$ -25 $D =\!$ -98.9 (c 2.05, CHCl$_3$); $\nu$H NMR (400 MHz) $\delta$ 8.03 (m, 2 H), 7.54 (m, 1 H), 7.42 (m, 2 H), 6.16 (m, 1 H), 5.95 (m, 2 H), 2.60 (m, 1 H), 2.39 (m, 2 H), 1.98 (m, 1 H); $\nu$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 166.5 (s), 137.6 (d), 132.6 (d), 130.6 (s), 129.5 (d), 129.3 (d, 2 x C), 128.2 (d, 2 x C), 81.0 (d), 31.1 (t), 29.8 (t); exact mass m/z calcld C$_{12}$H$_{12}$O$_2$ 188.08372, found 188.08463; HPLC analysis indicated an enantiomeric excess of 97% [Chiralcel OD-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99.9:0.1; $\lambda$ = 225 nm; major enantiomer (–)-5.41, $t_R =\!$ 18.57 min; minor enantiomer (+)-5.41, $t_R =\!$ 30.42 min, 97% ee; Chiralcel OD column; flow: 1 mL/min; n-heptane/i-PrOH: 99.5:0.5; $\lambda$ = 220 nm; major enantiomer (–)-5.41, $t_R =\!$ 6.43 min; minor enantiomer (+)-5.41, $t_R =\!$ 7.10 min, 97% ee]. The absolute configuration was assigned by comparison of optical rotation of known 5.26.

Phosphoramidite L1 (26.1 mg, 47 µmol) and CuTC (8.0 mg, 43 µmol) were added to a stirred solution of 5.53 (218 mg, 0.859 mmol) in CH$_2$Cl$_2$ (2 mL) under a nitrogen atmosphere. Stirring at room temperature was continued for 30 min before the reaction mixture was cooled to –70 °C. A solution of EtMgBr (3.0 M in diethyl ether, 0.57 mL, 1.7 mmol) was diluted with CH$_2$Cl$_2$ (1.2 mL), and the Grignard (now ca 1M in 2 mL CH$_2$Cl$_2$-ether) was then injected slowly via syringe pump over 1.5 h. Although TLC (5% EtOAc/n-pentane) analysis showed the reaction had reached completion after a further 30 min, stirring at –70 °C was continued overnight before the reaction was quenched with EtOH (5 mL). The reaction mixture was removed from the cooling bath and sat. aq. NH$_4$Cl (ca. 5 mL) was added. The mixture was partitioned between CH$_2$Cl$_2$ (5 mL) and water, and the organic layer dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. Flash chromatography of the residue over silica gel, using Et$_2$O/n-pentane mixtures from 0-5% Et$_2$O, gave a mixture of 5.60 and 5.61 (170 mg, 97 %) as a 2.5:1 mixture contaminated with traces ($\nu$H NMR spectroscopy) of L1. Ee determination using the method indicated below requires complete removal of L1 and chiral ligand due to overlapping retention times. Repeated flash chromatography provided a sample free of 5.61 ($\nu$H NMR spectroscopy), which was then distilled (Kugelrohr, 7 mmHg, oven ca 200 °C) to remove traces of L1. Pure 5.60 had: $\nu$H NMR (400 MHz) 8.08 (m, 2 H), 7.56 (m, 1 H), 7.45 (m, 2 H), 5.37 (t, $J$ = 6.6 Hz, 1 H), 5.04 (s, 1 H), 4.94 (s, 1 H), 1.80 (m, 5 H), 0.96 (t, $J$ = 7.4 Hz, 1 H); $\nu$C NMR (CDCl$_3$ 100.6 MHz) $\delta$ 165.7(s), 142.8 (s), 132.7 (d), 130.5 (s), 129.5 (d 2 x C), 128.2 (d 2 x C), 112.7 (s), 79.0 (d), 25.6 (t), 18.1 (q), 9.6 9 (q);
exact mass m/z calc for C_{12}H_{14}O_{2} = 204.11502, found 204.11557; HPLC analysis indicated an enantiomeric excess of 97% [Chiralcel OB-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99:1; λ = 207 nm; major enantiomer 5.60, t_R = 8.94 min; minor enantiomer 5.60, t_R = 11.24 min].

**Benzoic acid 1-isopropenylhexyl ester (5.60b)**

Phosphoramidite L1 (23.2 mg, 43 µmol) and CuTC (7.5 mg, 39 µmol) were added to a stirred solution of 5.53 (200 mg, 0.780 mmol) in CH₂Cl₂ (2 mL) under a nitrogen atmosphere. Stirring at room temperature was continued for 30 min before the reaction mixture was cooled to -70 °C. A solution of penty1MgBr (1.2 M in diethyl ether, 1.3 mL, 1.56 mmol) was diluted with CH₂Cl₂ (2.6 mL), and the Grignard (now ca 0.4 M in 3.9 mL CH₂Cl₂-ether) was then injected slowly via syringe pump over 1 h. Stirring at -70 °C was continued overnight before the reaction was quenched with MeOH (3 mL). The reaction mixture was removed from the cooling bath and sat. aq. NH₄Cl (ca. 5 mL) was added. The mixture was partitioned between CH₂Cl₂ (5 mL) and water, and the organic layer dried (MgSO₄), filtered and the solvent evaporated in vacuo. Flash chromatography of the residue over silica gel, using Et₂O/n-pentane mixtures from 0-5% Et₂O, gave a mixture of 5.60b and 5.61b (185 mg, 96 %) as a 2:1 mixture contaminated with traces (¹H NMR spectroscopy) of L1. Distillation (Kugelrohr, 7 mmHg, oven ca 250 °C) removed the traces of L1. Flash chromatography provided a sample significantly enriched (6:1) in 5.60b, so that it was suitable for HPLC analysis on a chiral non-racemic stationary phase. Signals corresponding to 5.60b (from spectra of the mixture by comparison with those of the pure racemate); ¹H NMR (400 MHz) δ 8.15–8.08 (m, 2 H), 7.61–7.53 (m, 1 H), 7.49–7.43 (m, 2 H), 5.46 (t, J = 6.4 Hz, 1 H), 5.06 (s, 1 H), 4.94 (s, 1 H), 1.85–1.79 (m, s H), 1.82 (s, 3 H), 1.50–1.25 (m, 6 H), 0.95–0.85 (m, 3 H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 165.7 (s), 143.2 (s), 132.7 (d), 130.6 (s), 129.5 (d, 2 x C), 128.4 (d, 2 x C), 112.6 (s), 77.9 (d), 32.6 (t), 31.5 (t), 25.0 (t), 22.5 (t), 18.1 (q), 14.0 (q); exact mass m/z calc for C_{12}H_{14}O_{2} = 246.16192; found 246.16192; HPLC analysis indicated an enantiomeric excess of 98% [Chiralcel OB-H column; flow: 0.5 mL/min; n-heptane/i-PrOH: 99.75:0.25; λ = 230 nm; major enantiomer 5.60b, t_R = 10.49 min; minor enantiomer 5.60b, t_R = 13.46 min.

(E)-(S)-Benzoic acid 4-bromo-1-methylbut-2-enyl ester (5.86)

Hoveyda Grubbs 2nd generation catalyst (15.0 mg, 0.024 mmol) was tipped into a stirred and degassed (3x) solution of 1,4-dibromo-2-butene (617.0 mg, 2.89 mmol) and 5.16 (106 mg, 0.62 mmol) in CH₂Cl₂ (5 mL) under a nitrogen atmosphere and flask was degassed another 2x. After 5 h another amount of Hoveyda Grubbs 2nd generation catalyst (16.2 mg, 0.026 mmol) was added and the reaction was degassed 2x. The mixture was stirred for 20 h before the solvent was evaporated in vacuo. Flash chromatography of the residue over silica gel, using Et₂O/n-pentane mixtures
from 0-10% Et₂O, gave 5.87 (117.2 mg, 77%) as a clear colorless oil; ¹H NMR (400 MHz) δ 8.07–8.03 (m, 2 H), 7.59–7.53 (m, 1 H), 7.47–7.41 (m, 2 H), 6.00 (dtd, J = 8.2, 7.2, 7.1, 1.0 Hz, 1 H), 5.89 (tdd, J = 15.3, 5.6, 0.79, Hz, 1 H), 5.67–5.59 (m, 1 H), 4.00–3.90 (m, 2 H) 1.46 (d, J = 6.53 Hz, 3 H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 165.5 (s), 134.3 (d), 132.9 (d), 130.2 (s), 129.5 (d, 2 x C), 128.3 (d, 2 x C), 127.7 (d), 70.0 (d), 31.6 (t), 20.0 (q); [α]$_{D}^{28}$ = +18.7 (c 0.44, CHCl₃); LRMS (Cl) m/z: 305 (M+Cl)$^+$, 286 ((M+NH₄)$^+$, 100).
5.10 References and notes


