Enantioselective copper catalyzed allylic alkylation using Grignard reagents; Applications in synthesis
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Chapter 3
Synthesis of chiral bifunctional building blocks through asymmetric allylic alkylation

In this chapter the application of the enantioselective copper catalyzed allylic alkylation (Cu-AAA) with Taniaphos L1 as a ligand in the synthesis of chiral bifunctional building blocks is described. Utility of an asymmetric catalytic reaction depends in part on the applicability of more complex substrates. The reaction was performed on allylic bromides with a protected hydroxyl or amine functional group using a range of Grignard reagents. High regio- and enantioselectivities were obtained with these functionalized substrates. The terminal olefin moiety in the products was transformed into a diverse range of functional groups without racemisation, providing facile access to a variety of versatile bifunctional chiral building blocks.

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3.1 Introduction

The complexity of natural products and pharmaceutical compounds, which is currently a major challenge to synthetic chemists, provides a strong incentive toward the design of catalytic methods, which enable access to versatile multifunctional enantioenriched building blocks and chiral starting materials, also. Retrosynthetic analysis of natural products frequently leads to bifunctional synthons, which contain a single stereogenic centre. Among the methods available to prepare these synthons, enantioselective catalysis is particularly attractive due to the ready accessibility of both enantiomers, the potential atom efficiency of such reactions, and the ease with which small variations in the product can be introduced. However, resolution, chiral pool or auxiliary based asymmetric syntheses are still the most widely applied approaches. That the more widespread use of catalytic approaches, the so called “catalytic switch”, over non-catalytic syntheses has not yet happened is due, in part, to the fact that new enantioselective catalytic methods are developed using benchmark substrates and not the building blocks required in, e.g. total synthesis. The organic chemists’ familiarity with chiral pool strategies and aversion to synthesizing chiral ligands, which must themselves be prepared enantiomerically pure, in case they are expensive or not commercially available, may be another reason that catalytic asymmetric methods are not routinely used.

![Scheme 3.1: Concept of the stereoselective synthesis of chiral bifunctional building blocks via Cu-catalyzed asymmetric allylic alkylation; FG = functional group; LG = leaving group.](image)

As discussed in chapter 1, copper catalyzed asymmetric allylic alkylation presents an opportunity to use hard organometallic-based nucleophiles, thus enabling the introduction of simple alkyl fragments at the γ-position. This provides branched chiral products that contain a terminal olefin functionality, which can be transformed subsequently into a broad
range of functional groups, derived from prochiral monosubstituted allylic substrates (Scheme 3.1). The inclusion of a functional group in the allylic precursor would offer access to a broad range of synthetically valuable bifunctional chiral building blocks.

3.1.1 Functionalised substrates in the Cu-AAA

In general, catalytic asymmetric reactions are developed using benchmark substrates. This is, perhaps, primarily due to their commercial availability and their supposed “well-behavedness”, i.e. ready enantiodiscrimination and inertness of the substituents on the reactive moiety. The preferred benchmark substrates for the copper catalyzed allylic alkylation have been cinnamyl or cyclohexyl based allylic compounds (Figure 3.1). After the development of conditions, which catalyze efficiently the allylic alkylation of, for instance, cinnamyl bromide, a broad substrate scope of other aromatic substrates can usually be applied (see, for example, chapter 2), although different types of substrate might not behave similarly.

![Figure 3.1: Typical allylic benchmark substrates for the copper catalyzed asymmetric allylic alkylation: cinnamyl-1 and cyclohexyl-based 2 allylic electrophiles.](image)

If an enantioselectively catalyzed reaction is suggested to be applicable in total synthesis, it is necessary to prove the applicability of the reaction to more complex systems. The introduction of functionality in the substrate can easily interfere with catalysis either showing lability of the functional group under the reaction conditions or through complexation of the catalyst to the functional group.

A good example of a functionalised substrate, where interference or lability of the functional group is imagined easily, is the allylic phosphate 3, which Hoveyda and co-workers have used successfully on several occasions (Scheme 3.2). The ester group at the γ-position can allow 1,2-addition or conjugate addition among other possibilities. Using their copper catalyst system with modular peptidic Schiff base ligands, they were able to obtain
products 4 in good yield and excellent selectivity, though. The reaction could be performed on allylic phosphates, bearing a disubstituted (R’ = H) as well as a trisubstituted (R’ = Me, Ph) olefin, allowing the formation of both tertiary and quaternary stereocenters.4

Scheme 3.2: Cu-catalyzed asymmetric allylic alkylation with allylic phosphates bearing an ester functionality at the γ-position.

Woodward and coworkers employed substrates 5, which are derived readily from Baylis-Hillman products (Scheme 3.3).5 These substrates have an ester group at the β-position and could be alkylated with full chemo- and regioselectivity using chiral secondary amines as ligands. EtZnCl, which is produced during the reaction, has a detrimental effect on the selectivity. Addition of MAO biased the Schlenk equilibrium of the organozinc compounds in favour of the dialkylzinc species and thus enantioselectivities up to 90% were attained. However, it is possible that this is not an allylic alkylation. A conjugate addition / elimination mechanism cannot be excluded. The absence of the other regioisomer, the S_N2-product, even under conditions that provide a less active and selective reaction indicates that this is a distinct possibility.

Scheme 3.3: Cu-catalyzed asymmetric allylic alkylation with allylic chlorides bearing an ester functionality at the β-position.

Linear aliphatic substrates 6, which contain a TBS-protected hydroxyl group at the δ-position, have been used by the group of Okamoto (Scheme 3.4).6 The enantioselectivity they achieved in the allylic alkylation using
Grignard reagents with a carbene-CuCl complex as the catalyst was modest, though. It was interesting to note that the $E$ and $Z$ isomers of the substrate yielded opposite enantiomers of the product.

Scheme 3.4: Cu-AAA with allylic substrates bearing a protected alcohol at the $\delta$-position.

Substrates bearing two enantiotopic leaving groups at an allylic position at either side of the alkene double bond are especially interesting targets. After $S_N2'$ substitution the unreacted leaving group becomes unreactive to allylic alkylation, although it can be a versatile handle for subsequent transformations. For example 1,4-dihalobut-2-enes 8, which were applied in the Cu-AAA by Alexakis and coworkers, furnish chiral homoallylic halides in excellent enantioselectivity (Scheme 3.5).  

Scheme 3.5: Cu-AAA with substrates containing enantiotopic allylic leaving groups.

Complete regioselectivity was reported. However, $S_N2$-substitution would produce a compound, which is still an allylic electrophile and the presence or absence of dialkylated products was not noted by the authors.
The versatile compounds 9 can serve as electrophiles and (through umpolung) as nucleophiles in subsequent reactions.

The cyclic *meso*-diphosphates 10 were applied successfully in copper catalyzed allylic alkylations with dialkylzinc reagents by the group of Gennari.8 These desymmetrisation reactions yield cyclic products with two stereogenic centers and a phosphate protected alcohol group. The particularly interesting product 12 could be obtained in an enantiomeric excess of up to 86%; in this case four new stereogenic centers have been formed in one step from an achiral precursor.

3.1.2 Heteroatoms at the γ-position; the *h*-AAA

Recently, a completely new type of substrate for the copper catalyzed allylic alkylation was introduced. Compounds with a heteroatom substituent at the γ-position had been deemed too unstable under the reaction conditions of allylic alkylation. However, in 2006 Geurts et al. reported the synthesis of chiral allylic esters through asymmetric allylic alkylation of 3-bromopropenyl benzoate 13 (Scheme 3.6).9 This transformation was coined hetero-allylic asymmetric alkylation, *h*-AAA.

![Scheme 3.6: The first example of a copper catalyzed enantioselective allylic alkylation on a substrate bearing a heteroatom substituent on the γ-position (*h*-AAA).](image)

The reasons for the perception of instability were primarily that ester groups can undergo 1,2-addition, vinyl esters are well-known acyl transfer agents and finally an oxygen atom at the γ-position might perturb the electronic properties of the allyl electrophile substantially. Nevertheless, substrate 13 was applied in the allylic alkylation under the conditions described previously in chapter 2. Using Taniaphos L1 as a ligand, various alkyl Grignard reagents and substrates were applied successfully; the desired allylic esters were obtained in excellent regio- and enantioselectivity.
Following this first example of a Cu-catalyzed \( h \)-AAA, allylic alkylations on compounds with silicon or boron substituents at the \( \gamma \)-position were reported, thus enabling the synthesis of chiral allyl silanes and boronates, respectively (Figure 3.2).\(^{10}\) This clearly demonstrates that the functional group tolerance and the generality of the asymmetric allylic alkylation is much larger than was envisioned previously.

Figure 3.2: Chiral allylsilanes and allylboronates obtained through \( h \)-AAA.

3.1.3 The relevance of bifunctionality in asymmetric allylic alkylation products in total synthesis

Despite the recent demonstration of the high functional group tolerance of copper catalyzed asymmetric allylic alkylation reactions (\textit{vide supra}), it has not yet found widespread application in synthesis. The preparation of building blocks, which can be used for total synthesis, usually relies on the presence of two or more functional groups as handles for further transformation. The functionality embedded in the substrate for the allylic alkylation can serve as one handle, the terminal olefin as another, since there are many transformations, which render a range of other functional groups from terminal alkenes.

In some cases, it is not necessary to obtain bi- or multifunctional building blocks from the enantioselective reaction, \textit{i.e.} when the synthesized building block already approaches the structure of the target close enough. For example, this is the case with natural compounds which have a terminal olefin next to a stereogenic center. One such compound is sporochnol \( 18 \), a fish deterrent (a fish-repelling agent), which was synthesized by Hoveyda and coworkers in two steps from allylic substrate \( 17 \) using a Cu-catalyzed enantioselective allylic alkylation and a deprotection of the tosylated alcohol (Scheme 3.7).\(^{11}\).
Another exception is when only the olefin needs to be transformed and the rest of the structure was already present in the substrate. Alexakis and coworkers used their copper catalyzed allylic alkylation to synthesize 20, a potential precursor to naproxen, which is a well-known anti-inflammatory drug (Scheme 3.8). The authors claimed its formal total synthesis, the last step being an oxidation of the double bond to a carboxylic acid, which was apparently deemed obvious. Despite the fact that several methods exist to accomplish such a transformation, the oxidation was not reported by the authors nor did they refer to one in the literature. The incompatibility of many of these well-known methods with naphthyl groups renders the transformation not that obvious, though. Although this cannot be found using conventional databases, the intended reaction has been accomplished with NaIO₄ and KMnO₄.
Other examples of formal total syntheses are those of two cyclic chiral imides reported by the group of Hoveyda: ethosuximide, an anti-convulsant, and aminoglutethimide, which has been used effectively against breast cancer. In these cases the necessity of bifunctionality in the building blocks obtained is clear. Transformation of the terminal olefin of the product, affords the intermediates needed to synthesize the target compounds (Scheme 3.9). The functionality, which was embedded in the substrate, is converted either in the same step (as in the case of ethosuximide) or at a later stage in the synthesis route (aminoglutethimide).

The total synthesis of (+)-baconipyrone C, performed by Hoveyda and coworkers, is the last example of the application of copper catalyzed enantioselective allylic alkylation in total synthesis in this section. It contains an elegant double allylic alkylation of compound 25 using trimethylaluminum and a N-heterocyclic carbene as the ligand (Scheme 3.10).

The general selectivity of the reaction is not particularly high, because in the second alkylation, catalyst control has to overcome substrate control. This led to substantial amounts of the meso-diastereomer (8%) and the regioisomer (27%), which underwent a sequential $S_{N}2'/S_{N}2$ substitution. The desired stereoisomer 26, separable from its byproducts by chromatography, could be obtained in 61% yield, though. Since two
enantioselective reactions have taken place, the enantiomeric excess of the product is excellent. The two geminally disubstituted alkenes are converted into ketones through ozonolysis and the alcohol is deprotected to yield the intermediate, which can be coupled to the other part of the target molecule.

Scheme 3.10: Double copper catalyzed allylic alkylation step using trimethyl aluminum in the total synthesis of baconipyrone C.
3.2 Results and Discussion

3.2.1 Asymmetric allylic alkylation on functionalised substrates

The compatibility of substrates containing either a protected hydroxyl or amine moiety with the reaction conditions of the allylic alkylation using Grignard reagents and the ligand Taniaphos \textbf{L1} was demonstrated using allylic bromides 28-30 (Table 3.1). The substrates 28\textsuperscript{15} and 29\textsuperscript{16} were synthesized in one step from 1,4-dibromobut-2-ene (Scheme 3.11). Substrate 30\textsuperscript{17} was prepared in three steps from 2-butyne-1,4-diol.

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node (A) at (0,0) {\textbf{28}};
\node (B) at (2,0) {\textbf{29}};
\node (C) at (4,0) {\textbf{30}};
\path[draw] (A) edge[i] node[above] {i} (B);
\path[draw] (B) edge[ii] node[above] {ii} (C);
\end{scope}
\end{tikzpicture}
\end{center}

\textit{Scheme 3.11: Synthesis of allylic bromides bearing functional groups at the \(\delta\)-position;}
\begin{itemize}
  \item i) BnOH, 10 mol\% \textit{n-}Bu\textsubscript{4}NHSO\textsubscript{4}, \textit{CH\textsubscript{2}Cl\textsubscript{2}}, aq. NaOH, rt, 44\%;
  \item ii) Ts(Boc)NH, K\textsubscript{2}CO\textsubscript{3}, MeCN, reflux, 54\% based on amide;
  \item iii) LiAlH\textsubscript{4}, THF, reflux, 69\%;
  \item iv) TBDPSCl, \textit{n-}BuLi, THF, reflux, 24\%;
  \item v) NBS, Me\textsubscript{2}S, CH\textsubscript{2}Cl\textsubscript{2}, rt, 57\%.
\end{itemize}

Compounds 28 and 29, subjected to methylmagnesium bromide in CH\textsubscript{2}Cl\textsubscript{2} at \(-75^\circ\text{C}\) in the presence of 1 mol\% of the chiral Cu-catalyst, undergo substitution to provide the products 31 and 32, respectively, in high yields and excellent regioselectivities (Table 3.1, entries 1 and 2). The reactions were performed on a preparative scale (7.5 mmol) to demonstrate their potential synthetic utility. The enantiomeric excesses of 31 and 32 were found to be 92\% and 95\%, respectively, after derivatization.\textsuperscript{18} The other allylic alkylations were performed on a smaller scale and with 5 mol\% catalyst loading for synthetic convenience. For example substrate 30,
containing a tert-butyl diphenylsilyl ether, could be methylated in high yield, excellent regioselectivity and with an enantiomeric excess of 94% (entry 3).

Table 3.1: Cu-catalyzed allylic alkylation with Grignard reagents of allylic bromides containing protected hydroxyl and amine functional groups.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>FG</th>
<th>RMgBr</th>
<th>product</th>
<th>yield(^b) (%)</th>
<th>b / l(^c)</th>
<th>ee(^d) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^e/)</td>
<td>28 BnO</td>
<td>MeMgBr</td>
<td>31</td>
<td>94</td>
<td>100:0</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>2(^e/)</td>
<td>29 Boc(Ts)N</td>
<td>MeMgBr</td>
<td>32</td>
<td>96</td>
<td>&gt;95:5</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30 TBDPSO</td>
<td>MeMgBr</td>
<td>33</td>
<td>72</td>
<td>&gt;95:5</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>4(^f)</td>
<td>28 BnO</td>
<td>EtMgBr</td>
<td>34</td>
<td>98</td>
<td>98:2</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>29 Boc(Ts)N</td>
<td>EtMgBr</td>
<td>35</td>
<td>83</td>
<td>&gt;95:5</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>28 BnO</td>
<td>n-BuMgBr</td>
<td>36</td>
<td>93</td>
<td>100:0</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>28 BnO</td>
<td>n-PentMgBr</td>
<td>37</td>
<td>87</td>
<td>100:0</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>28 BnO</td>
<td>3-butenylMgBr</td>
<td>38</td>
<td>89</td>
<td>&gt;95:5</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>28 BnO</td>
<td>Ph(CH(_2))(_2)MgBr</td>
<td>39</td>
<td>86</td>
<td>&gt;95:5</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Reagents and conditions: RMgBr (1.5 equiv), CuBr-SMe\(_2\) (5 mol%), L\(_1\) (6 mol%), CH\(_2\)Cl\(_2\), -75°C. \(b\) Isolated yield. \(c\) Established by GC or NMR. \(d\) Established by chiral GC or HPLC. \(e\) Reaction performed on preparative scale (7.5 mmol substrate). \(f\) Reaction performed with 1 mol% cat. and 1.2 equiv RMgBr.

Other linear alkyl Grignard reagents could also be applied to these functionalized substrates, all with similar results. Substrates 28 and 29 can be ethylated efficiently, providing products 34 and 35 with high regioselectivity and excellent enantioselectivity (Table 3.1, entries 4 and 5).
The use of the other Grignard reagents with substrate 28 gave products 36-39 with excellent regio- and enantioselectivities also (entries 6-9).

### 3.2.2 Derivatizations of the allylic alkylation products

A range of derivatisation reactions of 31 and 32 were performed to demonstrate their versatility; providing a family of optically active bifunctional synthons (Schemes 3.12–3.14). The enantiomeric purity of all bifunctional synthons was determined independently by GC or HPLC-analysis, to ensure that racemisation during the derivatisation did not occur.

#### 3.2.2.1 Synthesis of bifunctional building blocks containing a protected alcohol

Hydroboration of 31 and subsequent treatment with H$_2$O$_2$ provides the mono-protected diol 40 (Scheme 3.12).$^{19,20}$ This compound has been used before in the total syntheses of (E)-vitamin K$_1$, $^{21}$ vitamin E, $^{22}$ and cylindrocyclophane F. $^{23}$

![Scheme 3.12: Synthesis of bifunctional chiral building blocks 40-43 containing a benzyl protected alcohol group from allylic alkylation product 31.](image)
The olefin 31 was converted to methyl ketone 41 using a catalytic Wacker oxidation.\textsuperscript{24} Thus, treatment of olefin 31 with PdCl\textsubscript{2} (5 mol\%) and CuCl (2 equiv) under an O\textsubscript{2}-atmosphere provided β-hydroxyketone 41 in 86\% yield. This ketone has been applied in the total syntheses of the C\textsubscript{1}-C\textsubscript{25} segment of spirastrellolide A,\textsuperscript{25} the octalactins A and B,\textsuperscript{26} (+)-miyakolide,\textsuperscript{27} (−)-botryococcene\textsuperscript{28} and also (+)-phyllanthocin and (+)-phyllanthocindiol.\textsuperscript{29}

By carrying out an ozonolysis / NaBH\textsubscript{4} reduction protocol, 31 was converted into the mono-protected 1,3-diol 42.\textsuperscript{30} This simple building block has been applied in numerous total syntheses. Amongst the many recent examples are syntheses of potential antitumor agents,\textsuperscript{31} antibiotics,\textsuperscript{32} matrix metalloproteinase inhibitors\textsuperscript{33} and tetrahydrocannabinol analogues.\textsuperscript{34}

The β-hydroxyacid 43, which has been used in the synthesis of clasto-lactacystin β-lactone,\textsuperscript{35} was obtained in 52\% yield through Ru-catalyzed oxidation of the terminal olefin with NaIO\textsubscript{4}.\textsuperscript{36} From the representative examples shown in Scheme 3.12 it is evident that the catalytic asymmetric allylic alkylation of 28 can provide a variety of important difunctionalized synthons in a few steps. All products were shown by chiral GC or HPLC analysis to have retained the high ee (92\%) of the original allylic alkylation product 31.

### 3.2.2.2 Synthesis of bifunctional building blocks containing a protected amine

Compound 32 was detosylated by treatment with magnesium in methanol under sonication\textsuperscript{37} to yield Boc-protected amine 44 (Scheme 3.13). As for 41, the β-aminoketone 45 was obtained in 82\% yield using the same procedure for a catalytic Wacker oxidation.

In an analogous fashion to 42, compound 32 could be transformed using the ozonolysis / reduction protocol into either 1,3-aminoalcohol 46 or compound 47, depending on the work-up procedure. Direct quenching of the reaction with 1M aq. HCl gave exclusively compound 46. In contrast, prior concentration of the reaction mixture at 50°C (e.g. by removal of solvent in vacuo) led to a [1,5]-migration of the Boc-group to the newly formed alcohol,\textsuperscript{38} thus yielding compound 47, which contains a tosyl-protected amine and an alcohol with a Boc-protecting group. The full
The β²-amino acid 48 could be synthesized in 79% yield (Scheme 3.14), using the same Ru-catalyzed oxidation that furnished 43. This is especially noteworthy as β²-amino acids are in general difficult to obtain. The latter product was converted to the respective methyl ester 49, using TMSCHN₂ and MeOH and consecutively detosylated with Mg-powder and sonication to obtain N-Boc-protected β²-amino acid 50. This compound has been applied in the total synthesis of the potent antitumor macrolides cryptophycin A, B and C.

The transformations described in schemes 3.13 and 3.14 show that the allylic alkylation product 32 is an attractive precursor for (protected) amino acid functionalization. The high selectivity of either method increases significantly the versatility of this building block precursor.
alcohols, amino ketones and $\beta^2$-amino acids. Similar transformations are readily accomplished with allylic alkylation products (e.g. compound 35) obtained with other Grignard reagents. All derivatives shown in schemes 3.13 and 3.14 were obtained with the same high enantiomeric excess (95%) as product 32. This was determined by GC or HPLC analysis.

Scheme 3.14: Synthesis of $\beta^2$-amino acid building blocks from product 32.
3.3 Conclusions

In conclusion, it has been demonstrated that the Cu-catalyzed allylic alkylation with Grignard reagents can be performed with excellent yield, regioselectivity and enantioselectivity on allylic bromides bearing protected functional groups on the δ-position. In addition, two of the reactions have been performed on a preparative scale (more than 1 gram), showing their versatility in synthetic organic chemistry.

The products obtained were shown to be suitable precursors in the synthesis of optically active bifunctional building blocks within one or two steps. Many of these bifunctional building blocks have demonstrated their value already through multiple applications in the total synthesis of natural products. This catalytic protocol makes use of a commercially available chiral ligand and is thus easily applicable for practicing organic chemists. This access to a wide variety of versatile bifunctional building blocks provides an important alternative to common approaches using chiral synthons derived from the chiral pool.
3.4 Experimental Part

General Remarks: For general remarks, see the experimental part of chapter 2. In addition, the following remarks should be taken into account:

The substrates 28, 29, and 30 were prepared according to literature procedures. THF was distilled from Na/benzophenone and CH\textsubscript{2}Cl\textsubscript{2} was distilled from CaH\textsubscript{2}. All other solvents were used as purchased.

Racemic products of derivatization reactions were obtained through the transformations described, vide infra, on the racemic allylic alkylation products. The products 31, 33, 36, 40, 41, 42, 43, and 50 have been previously described elsewhere (for appropriate references vide infra).

General Procedure for the Preparative Enantioselective Cu-catalyzed Allylic Alkylation with Methyl Grignard: In a Schlenk tube equipped with septum and stirring bar, CuBr\cdot SMe\textsubscript{2} (75 μmol, 15.4 mg) and ligand L\textsubscript{1} (90 μmol, 61.9 mg) were dissolved in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) and stirred under an argon atmosphere at room temperature for 10 min. The mixture was cooled to –75 °C and the methyl Grignard reagent (9.0 mmol, 3M solution in Et\textsubscript{2}O, 3.0 mL) was added dropwise. Allylic bromide 28 or 29 (7.5 mmol) was added dropwise as a solution in 2.5 mL CH\textsubscript{2}Cl\textsubscript{2} at that temperature over 60 min via a syringe pump. Once the addition was complete, the resulting mixture was stirred at –75 °C for a further 24 h. The reaction was quenched by addition of MeOH (2.5 mL) and the mixture was allowed to reach rt. Subsequently, aqueous NH\textsubscript{4}Cl solution (1M, 30 mL) and 50 mL Et\textsubscript{2}O were added, the organic phase was separated and the resulting aqueous layer was extracted with Et\textsubscript{2}O (2x 25 mL). The combined organic phases were dried and concentrated to yield a yellow oil which was purified by flash chromatography.

(−)-(S)-((2-Methylbut-3-enyloxy)methyl)benzene (31):\textsuperscript{41}

\[
\text{Purification by column chromatography (SiO}_2, 1.99 \text{ Et}_2\text{O/n-pentane, R}_f = 0.35 \text{ afforded 31 (1.24 g) as a colourless oil. [94% yield, 92% ee, [\alpha]_D = –5.4 (c 1.3, CHCl}_3); lit.}\textsuperscript{41a} [\alpha]_D = –3 (c 1.0, CHCl}_3); ¹H-NMR \delta 7.32-7.21 (m, 5H), 5.81 (ddd, J = 6.9, 10.4 and 17.3 Hz, 1H), 5.11-5.00 (m, 2H), 4.53 (s, 2H), 3.35 (ddd, J = 6.7, 9.1 and 23.9 Hz, 2H), 2.54-
2.49 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H); $^{13}$C-NMR δ 141.3, 138.6, 128.3, 127.5, 127.4, 114.0, 75.0, 72.9, 37.8, 16.6; MS (EI) m/z 176 (M+, 16), 175 (6), 92 (11), 91 (100), 65 (6); HRMS Calcd. for C$_{12}$H$_{16}$O 176.1201, found 176.1207. Enantiomeric excess determined for derivatized product 40.

(−)-(S)-(N-2-Methylbut-3-enyl)(N-t-butoxycarbonyl)p-toluene sulfonamide (32):

Purification by column chromatography (SiO$_2$, 10:90 Et$_2$O/n-pentane, R$_f$ = 0.30) afforded 32 (2.45 g) as a colourless oil. [96% yield, 95% ee, [α]$_D$ = −7.7 (c 1.4, CHCl$_3$)]; $^1$H-NMR δ 7.78 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.73 (ddd, J = 8.1, 10.2 and 17.3 Hz, 1H), 5.10-5.00 (m, 2H), 3.82-3.72 (m, 2H), 2.78-2.66 (m, 1H), 2.43 (s, 3H), 1.32 (s, 9H), 1.07 (d, J = 6.8 Hz, 3H); $^{13}$C-NMR δ 151.0, 144.0, 140.7, 137.5, 129.1, 127.9, 115.3, 84.0, 51.9, 38.7, 27.8, 21.5, 17.3; MS (EI) m/z 283 (9), 216 (20), 185 (6), 184 (64), 155 (42), 91 (39), 68 (7), 65 (11), 57 (100), 56 (5), 55 (13); MS (CI) m/z 359 (8), 358 (20), 357 ([M+NH$_4$]$^+$,100), 302 (7), 301 (40), 284 (6). HRMS Calcd. for [M-Me$_2$C=CH$_2$]$^+$ C$_{13}$H$_{17}$NO$_4$S 283.0878, found 283.0887. Enantiomeric excess determined for derivatized product 44. The absolute configuration was assigned by comparison of the sign of the optical rotation of derivatized product 50 with the literature value (vide infra).

General Procedure for the Enantioselective Cu-catalyzed Allylic Alkylations: In a Schlenk tube equipped with septum and stirring bar, CuBr·SMe$_2$ (15 μmol, 3.1 mg) and ligand L1 (18 μmol, 12.4 mg) were dissolved in CH$_2$Cl$_2$ (2.5 mL) and stirred under argon at room temperature for 10 min. The mixture was cooled to −75 °C and the Grignard reagent (0.45 mmol, solution in Et$_2$O) was added dropwise. The allylic bromide (0.3 mmol) was then added dropwise as a solution in 0.5 mL CH$_2$Cl$_2$ at −75 °C over 15 min. Once the addition was complete the resulting mixture was further stirred at −75 °C. After full conversion was established by TLC the reaction was quenched by addition of MeOH (0.5 mL) and the mixture was allowed to reach rt. Then, sat. aqueous NH$_4$Cl solution (1.5 mL) was added, the organic phase was separated and the aqueous phase was extracted with Et$_2$O (2x 2.5 mL). The combined organic phases were dried and
concentrated to yield a yellow oil, which was purified by flash chromatography.

\(-\)(-)-4-[(tert-Butyldiphenylsilyloxy)-3-methylbut-1-ene (33):\(^{41a}\)

\[\text{Purification by column chromatography (SiO} _2, 0.2:99.8 \text{ Et}_2\text{O/n-pentane, } R_f = 0.25) \text{ afforded 33 (70.3 mg) as a colourless oil. [72\% yield, 94\% ee, } \alpha\]D = \(-2.7 \text{ (c 1.3, CHCl}_3)\); lit.\(^{41a}\) \[\alpha\]D = \(-3.18 \text{ (94\% ee, c 0.71, CHCl}_3)\]; \(^{1}\text{H-NMR } \delta \text{ 7.68 (dd, } J = 7.7 \text{ and 1.6 Hz, 4H), 7.45-7.36 (m, 6H), 5.81 (ddd, } J = 6.9, 10.4 \text{ and 17.4 Hz, 1H), 5.06-4.98 (m, 2H), 3.58 (dd, } J = 9.7 \text{ and 6.2 Hz, 1H), 3.50 (dd, } J = 9.7 \text{ and 6.7 Hz, 1H), 2.44-2.37 (m, 1H), 1.06 (s, 9H), 1.04 (d, } J = 6.8 \text{ Hz, 3H); } \^{13}\text{C-NMR } \delta \text{ 141.3, 135.6, 133.9, 129.5, 127.6, 114.0, 68.5, 40.2, 26.9, 19.3, 16.2; MS (EI) } m/z \text{ 268 (24), 267 ([M-tBu]+, 100), 240 (17), 239 (80), 237 (12), 211 (9), 199 (15), 197 (14), 190 (7), 189 (36), 183 (23), 182 (7), 181 (19), 159 (19), 135 (18), 121 (10), 105 (11), 77 (7); MS (CI) } m/z \text{ 344 (8), 343 (28), 342 ([M+NH}_4]+, 100), 325 ([M+H]+, 14). HRMS Calcd. for [M-tBu]+ } C_{17}H_{19}OSi 267.1205, \text{ found 267.1197. Enantiomeric excess determined for derivatized product 42 (Scheme 3.15, vide infra).}

(+)-1-((2-ethylbut-3-enyloxy)methyl)benzene (34):\(^{42}\)

\[\text{Purification by column chromatography (SiO} _2, 2:98 \text{ Et}_2\text{O/n-pentane) afforded a 98 : 2 mixture of 34 and and its regioisomer as a colorless oil. [97\% yield, 94\% ee, } \alpha\]D = \(+19 \text{ (c 1.1, CHCl}_3)\); \(^{1}\text{H-NMR } \delta \text{ 7.30-7.21 (m, 5H), 5.66-5.57 (m, 1H), 5.06-5.01 (m, 2H), 4.47 (s, 2H), 3.35 (d, } J = 6.5 \text{ Hz, 2H), 2.22 (m, 1H), 1.56-1.47 (m, 1H), 1.27-1.20 (m, 1H), 0.83 (t, } J = 7.5 \text{ Hz, 3H); } \^{13}\text{C-NMR } \delta \text{ 140.0, 138.6, 128.3, 127.5, 127.4, 115.6, 73.6, 73.0, 45.7, 24.0, 11.4; MS (EI) } m/z \text{ 190 (M+, 11), 189 (11), 123 (21), 105 (100), 91 (79), 77 (30); HRMS Calcd. for C}_{13}H_{18}O 190.13576, \text{ found 190.13505. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel OD-H (99.75\% } n\text{-heptane/iPrOH), 40ºC, retention times (min): 9.9 (minor) and 10.9 (major). In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.} \]
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(−)-(N-2-Ethylbut-3-enyl)(N-tert-butoxycarbonyl) p-toluenesulfonamide (35):

Purification by column chromatography (SiO2, 5:95 Et2O/n-pentane, Rf = 0.25) afforded 35 (87.5 mg) as a colourless oil. [83% yield, 91% ee, \([\alpha]_D = -0.4\) (c 8.5, CHCl3)]; 1H-NMR \(\delta\) 7.75 (d, \(J = 8.1\)Hz, 2H), 7.26 (d, \(J = 8.1\)Hz, 2H), 5.59-5.49 (m, 1H), 5.06-5.00 (m, 2H), 3.78 (d, \(J = 7.7\)Hz, 2H), 2.49-2.40 (m, 1H), 2.39 (s, 3H), 1.55-1.44 (m, 1H), 1.29 (s, 9H) ppm; 13C-NMR \(\delta\) 151.0, 143.9, 139.3, 137.5, 129.0, 127.8, 117.2, 83.9, 50.8, 46.7, 27.7, 24.8, 21.5, 11.5; MS (EI) \(m/z\) 353 (M+, 0.1), 297 (15), 216 (10), 185 (9), 184 (88), 155 (49), 92 (5), 91 (39), 82 (39), 69 (7), 65 (9), 57 (100); MS (CI) \(m/z\) 373 (9), 372 (20), 371 ([M+NH4]+, 100), 317 (6), 316 (12), 315 (75), 298 (8), 271 (8). HRMS Calcd. for [M-Me2C=CH2]+ C14H19NO4S 297.1035, found 297.1027. Enantiomeric excess determined for derivatized product 51. In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.

(+)-(S)-(2-n-Butylbut-3-enyloxy)methylbenzene (36):

Purification by column chromatography (SiO2, 1:99 Et2O/n-pentane, Rf = 0.50) afforded 36 (60.5 mg) as a colorless oil. [93% yield, 94% ee, \([\alpha]_D = + 18.5\) (c 2.2, CHCl3)]; 1H-NMR \(\delta\) 7.38-7.27 (m, 5H), 5.70 (ddd, \(J = 8.4, 10.6\) and 17.0Hz, 1H), 5.13-5.07 (m, 2H), 4.54 (s, 2H), 3.42 (d, \(J = 6.4\)Hz, 2H), 2.42-2.32 (m, 1H), 1.60-1.48 (m, 1H), 1.40-1.20 (m, 5H), 0.92 (t, \(J = 7.0\)Hz, 3H); 13C-NMR \(\delta\) 140.4, 138.6, 128.3, 127.5, 127.4, 115.4, 73.8, 72.9, 44.1, 30.9, 29.1, 22.8, 14.0; MS (EI) \(m/z\) 218 (M+, 11), 107 (13), 105 (6), 104 (7), 97 (8), 96 (6), 92 (15), 91 (100), 85 (11), 83 (16), 69 (6), 65 (8), 57 (8), 55 (21); HRMS Calcd. for C15H22O 218.1671, found 218.1665. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel OD-H (100% n-heptane), 40ºC, retention times (min): 11.6 (minor) and 13.6 (major). The absolute configuration was assigned by comparison of the sign of optical rotation of the hydrogenated product 2-ethylhexan-1-ol (Pd/C, H₂ in MeOH) with the literature value.43
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(+)-(S)-((2-n-Pentylbut-3-enyloxy)methyl)benzene (37):

Purification by column chromatography (SiO₂, 1:99 Et₂O/n-pentane, Rf = 0.50) afforded 37 (60.4 mg) as a colorless oil. [87% yield, 94% ee, [α]D = + 14.4 (c 2.4, CHCl₃)]; ¹H-NMR δ 7.38-7.28 (m, 5H), 5.70 (ddd, J = 8.4, 10.6 and 17.0Hz, 1H), 5.14-5.07 (m, 2H), 4.55 (s, 2H), 3.42 (d, J = 6.5Hz, 2H), 2.42-2.32 (m, 1H), 1.59-1.46 (m, 1H), 1.40-1.21 (m, 7H), 0.91 (t, J = 6.9Hz, 3H); ¹³C-NMR δ 140.4, 138.6, 128.2, 127.5, 127.4, 115.4, 73.8, 72.9, 44.1, 31.9, 31.2, 26.6, 22.6, 14.1; LRMS (EI) m/z 232 (M⁺, 24), 231 (6), 161 (7), 107 (8), 105 (5), 104 (11), 92 (14), 91 (100), 69 (14), 65 (5), 55 (8); HRMS Calcd. for C₁₆H₂₄O 232.1827, found 232.1835. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel OD-H (100% n-heptane), 40ºC, retention times (min): 11.5 (minor) and 13.3 (major). The absolute configuration was assigned by comparison of the sign of optical rotation of the hydrogenated product 2-ethylheptan-1-ol (Pd/C, H₂ in MeOH) with the literature value.⁴⁴

(+)-(S)-(2-Vinyl-hex-5-enyloxy)methyl)-benzene (38):

Purification by column chromatography (SiO₂, 1:99 Et₂O/n-pentane, Rf = 0.50) afforded 38 (57.5 mg) as a colorless oil. [89% yield, 90% ee, [α]D = + 10.0 (c 2.5, CHCl₃)]; ¹H-NMR δ 7.40-7.27 (m, 5H), 5.82 (tdd, J = 6.6, 10.2 and 16.9 Hz, 1H), 5.74-5.64 (m, 1H), 5.14-4.94 (m, 4H), 4.53 (s, 2H), 3.46-3.38 (m, 2H), 2.45-2.36 (m, 1H), 2.18-1.97 (m, 2H), 1.70-1.60 (m, 1H), 1.44-1.34 (m, 1H); ¹³C-NMR δ 139.9, 138.7, 138.5, 128.3, 127.5, 127.4, 115.8, 114.5, 73.7, 72.9, 43.5, 31.1, 30.4; MS (EI) m/z 216 (M⁺, 0.4), 173 (6), 95 (6), 92 (11), 91 (100), 79 (6), 67 (8), 65 (11), 55 (5); HRMS Calcd. for C₁₅H₂₀O 216.1514, found 216.1513. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel OD (100% n-heptane), 40ºC, retention times (min): 7.5 (minor) and 8.5 (major). The absolute configuration was assigned by comparison of the sign of optical rotation of the hydrogenated product 2-ethylhexan-1-ol (Pd/C, H₂ in MeOH) with the literature value.⁴³
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(+)-(2-Vinyl-4-phenyl-butyloxymethyl)-benzene (39):

Purification by column chromatography (SiO$_2$, 1:99 Et$_2$O/n-pentane, R$_f$ = 0.50) afforded 39 (69.0 mg) as a colorless oil. [86% yield, 92% ee, [$\alpha$]$_D$ = + 3.8 (c 2.2, CHCl$_3$)]; $^1$H-NMR $\delta$ 7.42-7.35 (m, 4H), 7.35-7.29 (m, 3H), 7.25-7.20 (m, 3H), 5.78 (ddd, $J$ = 8.5, 11.0 and 16.5Hz, 1H), 5.21-5.15 (m, 2H), 4.55 (s, 2H), 3.51-3.43 (m, 2H), 2.78-2.69 (m, 1H), 2.59 (ddd, $J$ = 6.6, 10.2 and 13.8Hz, 1H), 2.51-2.41 (m, 1H), 1.93 (ddd, $J$ = 4.6, 6.6, 11.1 and 13.4Hz, 1H), 1.70-1.60 (m, 1H); $^{13}$C-NMR $\delta$ 142.4, 139.8, 138.5, 128.4, 128.3, 128.2, 127.5, 127.4, 125.6, 116.1, 73.7, 72.9, 43.7, 33.2, 33.0; MS (EI) m/z 266 (M$^+$, 3), 162 (5), 157 (10), 129 (6), 104 (5), 92 (10), 91 (100), 65 (10); HRMS Calcd. for C$_{19}$H$_{22}$O$_2$ 266.1671, found 266.1682. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel OD (99.5% n-heptane/i-PrOH), 40°C, retention times (min): 8.1 (minor) and 10.0 (major). In accordance with the results obtained in the other allylic alkylations, the absolute configuration of this compound is assumed to be (S), analogous to the other products.

(+)-(S)-4-Benzylloxy-3-methylbutan-1-ol (40):$^{23b}$

To a cooled solution (0 °C) of 31 (0.5 mmol, 88 mg) in THF (3.5 mL) a solution of 9-BBN (0.75 mmol, 0.5M in THF, 1.5 mL) was added. The reaction mixture was stirred for 3 h, then it was allowed to reach rt, after which sequentially EtOH (2.5 mL), aq. NaOH (1M, 2.5 mL) and aq. H$_2$O$_2$ (30%, 2.0 mL) were added. The resulting mixture was stirred vigorously overnight at rt, then quenched with aq. Na$_2$S$_2$O$_3$ (10%, 10 mL). CH$_2$Cl$_2$ (20 mL) was added, the organic phase was separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (20 mL). The combined organic layers were dried and concentrated in vacuo. Purification by column chromatography (SiO$_2$, 40:60 Et$_2$O/n-pentane, R$_f$ = 0.25) afforded 40 (77.3 mg) as a colorless oil. [80% yield, 92% ee, [$\alpha$]$_D$ = + 1.8 (c 2.9, EtOH), − 5.5 (c 2.7, CHCl$_3$), lit.$^{21,22,45}$ [$\alpha$]$_D$ = + 2.2 (c 1.1, EtOH), + 6.26 (c 5.5, CHCl$_3$)]; $^1$H-NMR $\delta$ 7.39-7.26 (m, 5H), 4.52 (s, 2H), 3.75-3.61 (m, 2H), 3.35 (ddd, $J$ = 6.2, 9.1 and 16.5Hz, 2H), 2.42 (bs, 1H), 1.95 (tq, $J$ = 6.9 and 13.8Hz, 1H), 1.69-1.51 (m, 2H), 0.95 (d, $J$ = 6.9Hz, 3H); $^{13}$C-NMR $\delta$ 138.0, 128.4, 127.7, 76.1, 73.2, 61.2, 38.1, 31.4, 17.7; MS (EI)
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\[ m/z \ 194 \ (M^+, \ 7), \ 108 \ (11), \ 107 \ (37), \ 105 \ (6), \ 92 \ (28), \ 91 \ (100), \ 85 \ (12), \ 79 \ (7), \ 77 \ (8), \ 65 \ (15), \ 55 \ (8); \ \text{HRMS \ Calcd. \ for} \ C_{12}H_{18}O_2 \ 194.1307, \ \text{found} \ 194.1309. \ \text{Enantiomeric \ excess \ determined \ by \ chiral \ HPLC \ analysis,} \ \text{Chiralcel \ OD-H} \ (99\% \ n-\text{heptane/i-PrOH}), \ 40^\circ \text{C, retention \ times \ (min):} \ 57.7 \ (\text{major}) \ \text{and} \ 64.9 \ (\text{minor}). \]

\((-\text{R})\)-4-Benzylxoy-3-methylbutan-2-one (41):\(^{29,47}\)

![Image of chemical structure](image)

A suspension of PdCl\(_2\) (50 \(\mu\)mol, 8.9 mg) and CuCl (1.0 mmol, 99 mg) in DMF/H\(_2\)O (6:1, 5 mL) was stirred vigorously under an O\(_2\)-stream for 1.5 h at rt. After addition of 31 (0.5 mmol, 88 mg) vigorous stirring was continued for 32 h under an O\(_2\)-atmosphere at rt. Then, H\(_2\)O (20 mL) was added and the mixture was extracted with Et\(_2\)O/ pentane (1:1, 3x 10 mL). The combined organic layers were washed with H\(_2\)O (10 mL), dried and concentrated in vacuo. Purification by flash chromatography (SiO\(_2\), 10:90 Et\(_2\)O/ pentane, \(R_f = 0.20\)) afforded 41 (82.4 mg) as a colorless oil. \([86\% \ \text{yield, 92\% ee,} \ \left[\alpha\right]_D = -14.0 \ (\text{c} \ 4.0, \ \text{CHCl}_3), \ \text{lit.}^{29b} \ \left[\alpha\right]_D = -16.7 \ (\text{c} \ 39.1, \ \text{CHCl}_3)]\); \(^1\)H-NMR \(\delta\) 7.37-7.26 (m, 5H), 4.50 (d, \(J = 1.8\) Hz, 2H), 3.63 (dd, \(J = 7.5\) and 9.2 Hz, 1H), 3.49 (dd, \(J = 5.5\) and 9.2 Hz, 1H), 2.91-2.81 (m, 1H), 2.18 (s, 3H), 1.10 (d, \(J = 7.1\) Hz, 3H); \(^{13}\)C-NMR \(\delta\) 211.1, 138.0, 128.4, 127.6, 127.6, 73.2, 72.1, 47.2, 29.0, 13.4; MS (EI) \(m/z\) 192 (M\(^+\), 4), 134 (27), 108 (18), 107 (46), 105 (12), 92 (14), 91 (100), 86 (43), 85 (6), 79 (8), 77 (7), 71 (27), 65 (9); HRMS Calcd. for C\(_{12}\)H\(_{16}\)O\(_2\) 192.1150, found 192.1144. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel AS (99.5\% n-heptane/i-PrOH), 40°C, retention times (min): 11.8 (minor) and 16.4 (major).

\((-\text{S})\)-3-Benzylxoy-2-methylpropan-1-ol (42):\(^{48}\)

Ozone was bubbled for 10 min through a solution of 31 (0.5 mmol) in CH\(_2\)Cl\(_2\)/MeOH (1:1, 15 mL) cooled to \(-78^\circ\text{C}\). NaBH\(_4\) (2.5 eq., 2.5 mmol, 95 mg) was added at \(-78^\circ\text{C}\) after which the cooling bath was removed and the reaction mixture was stirred at rt for 2 h. The reaction was quenched by addition of aq. HCl (1M, 15 mL). The organic layer was separated and the resulting aqueous layer extracted with CH\(_2\)Cl\(_2\) (2x 25 mL) the combined organic layers were dried (MgSO\(_4\)) and concentrated in vacuo. Purification
by flash chromatography (SiO₂, 30:70 Et₂O/pentane, R_f = 0.30) afforded 42 (47.0 mg) as a colorless oil. [52% yield, 92% ee, [α]D = −13.0 (c 2.3, CHCl₃)]; ¹H-NMR δ 7.39-7.26 (m, 5H), 4.52 (s, 2H), 3.66-3.53 (m, 3H), 3.43 (dd, J = 8.0 and 9.0Hz, 1H), 2.56 (bs, 1H), 2.14-2.02 (m, 1H), 0.89 (d, J = 7.0Hz, 3H); ¹³C-NMR δ 138.0, 128.4, 127.6, 127.5, 75.1, 73.3, 67.5, 35.5, 13.4; LRMS (EI) m/z 180 (M⁺, 10), 108 (13), 107 (51), 105 (6), 92 (23), 91 (100), 89 (5), 79 (15), 78 (5), 77 (13), 65 (18), 51 (7); HRMS Calcd. for C₁₁H₁₆O₂ 180.1150, found 180.1157.

Enantiomeric excess determined by chiral HPLC analysis, Chiralcel AS (98.5% n-heptane/i-PrOH), 40ºC, retention times (min): 11.9 (minor) and 14.0 (major).

(−)-(R)-3-Benzylxy-2-methylpropionic acid (43):²⁹,⁴⁷

To a biphasic system of 31 (0.5 mmol) and NaIO₄ (2.05 mmol, 438 mg) in CCl₄/McCN/H₂O (1:1:1.5, 5 mL), RuCl₃·xH₂O (25 μmol, 5.2 mg) was added and the reaction was stirred vigorously overnight. Afterwards, 10 mL CH₂Cl₂ and 5 mL H₂O were added and the organic layer was separated, the aqueous layer was further extracted with CH₂Cl₂ (3x 5mL) and the combined organic layers were dried (MgSO₄) and concentrated in vacuo. The residue was dissolved in Et₂O (10 mL) and extracted with sat. aq. NaHCO₃ (3x 5 mL), the combined aqueous layers were acidified and extracted with CH₂Cl₂ (3x 10 mL). Drying (MgSO₄) and concentrating the combined CH₂Cl₂ layers in vacuo afforded 43 (50.3 mg) as a colorless oil. [52% yield, 92% ee, [α]D = −6.7 (c 2.7, CHCl₃)]; ¹H-NMR δ 10.78 (bs, 1H), 7.40-7.27 (m, 5H), 4.56 (s, 2H), 3.66 (dd, J = 7.5 and 9.0Hz, 1H), 3.55 (dd, J = 5.7 and 9.1Hz, 1H), 2.88-2.78 (m, 1H), 1.22 (d, J = 7.1Hz, 3H); ¹³C-NMR δ 180.8, 137.8, 128.3, 127.6, 127.6, 73.1, 71.5, 40.1, 13.7; MS (EI) m/z 194 (M⁺, 16), 108 (9), 107 (83), 105 (8), 92 (13), 91 (100), 89 (5), 79 (23), 77 (14), 73 (6), 65 (18), 51 (7); HRMS Calcd. for C₁₁H₁₄O₃ 194.0943, found 194.0948. Enantiomeric excess determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), isothermic 150 ºC, retention times (min): 41.5 (minor) and 42.9 (major).
(−)-(S)-(N-tert-Butoxycarbonyl)(2-methylbut-3-yl)amine (44):

To a solution of 32 (0.5 mmol, 170 mg) in MeOH (6 mL) Mg-powder (2.5 mmol, 61 mg) was added and the mixture was sonicated for 60 min at rt. The resulting suspension was diluted with CH2Cl2 (20 mL) and poured in aq. HCl (0.5 M, 20 mL). The organic phase was separated and washed with aq. sat. NaHCO3 (2x 10 mL), dried and concentrated in vacuo, affording 44 (83.3 mg) as a colorless oil. [90% yield, 95% ee, [α]D = −16.1 (c 2.7, CHCl3)]; 1H-NMR δ 5.67 (ddd, J = 7.6, 10.4 and 17.6 Hz, 1H), 5.09-5.02 (m, 2H), 4.54 (bs, 1H), 3.20-3.09 (m, 1H), 2.95 (ddd, J = 5.4, 8.0 and 13.3 Hz, 1H), 2.37-2.26 (m, 1H), 1.44 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H); 13C-NMR δ 155.9, 141.3, 114.9, 78.9, 45.6, 38.3, 28.3, 17.3; MS (EI) m/z 130 (6), 129 (19), 57 (100), 56 (7); MS (Cl) m/z 204 (13), 203 ([M+NH4]+, 100), 202 (5), 187 (7), 186 ([M+H]+, 58), 163 (9), 148 (5), 147 (63), 130 (33), 86 (7). HRMS Calcd. for [M-Me2C=CH2]+ C6H11NO2 129.0790, found 129.0797. Enantiomeric excess determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 85 ºC, rate 10 ºC/min., fin. temp. 120 ºC, retention times (min): 61.4 (major) and 64.7 (minor).

(+)-(R)-4-([tert-Butoxycarbonyl](p-toluenesulfonyl)amino)-3-methyl-butan-2-one (45):

The title compound was prepared in an analogous way to 41 from 32. Purification by flash chromatography (SiO2, 10:90 Et2O/pentane, Rf = 0.05) afforded 45 (145.3 mg) as a colorless oil. [82% yield, 95% ee, [α]D = +2.6 (c 7.1, CHCl3); 1H-NMR δ 7.77 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.04 (dd, J = 6.0 and 14.6 Hz, 1H), 3.90 (dd, J = 8.0 and 14.6 Hz, 1H), 3.16-3.02 (m, 1H), 2.43 (s, 3H), 2.21 (s, 3H), 1.31 (s, 9H), 1.21 (s, J = 7.2 Hz, 3H); 13C-NMR δ 210.1, 150.8, 144.2, 136.9, 129.1, 127.7, 84.4, 48.5, 47.1, 28.6, 27.6, 21.4, 14.2; MS (EI) m/z 282 ([M-tertBuO]+, 5), 200 (9), 198 (6), 191 (27), 184 (35), 156 (5), 155 (53), 144 (31), 120 (15), 108 (27), 102 (7), 100 (27), 91 (50), 72 (10), 65 (11), 61 (9), 58 (20), 57 (100), 56 (6); MS (Cl) m/z 375 (11), 374 (31), 373 ([M+NH4]+, 100), 317 (5), 219 (6), 69 (5). HRMS Calcd. for [M-tertBuO]+ C13H16NO4S 282.0800, found 282.0805. Enantiomeric excess
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determined by chiral HPLC analysis, Chiralcel AD (98% n-heptane/i-PrOH), 40°C, retention times (min): 16.8 (major) and 20.9 (minor).

\((-\rangle\rangle)-3-((tert-Butoxycarbonyl)(p-toluenesulfonyl)amino)-2-methylpropan-1-ol (46):

The title compound was prepared in an analogous way to 42 from 32. Purification by flash chromatography (SiO\textsubscript{2}, 50:50 Et\textsubscript{2}O/pentane, R\textsub{f} = 0.25) afforded 46 (132.8 mg) as a colorless oil, which crystallized upon standing. [77% yield, 95% ee, [\alpha]_D = -3.3 (c 8.1, CHCl\textsubscript{3}), mp = 59.8-60.4 °C]; \textsuperscript{1}H-NMR \delta 7.73 (d, \(J = 8.2\)Hz, 2H), 7.28 (d, \(J = 8.5\)Hz, 2H), 3.85 (dd, \(J = 9.1\) and 14.6Hz, 1H), 3.72 (dd, \(J = 5.3\) and 14.6Hz, 1H), 3.50-3.63 (m, 1H), 3.51-3.43 (m, 1H), 2.63 (bs, 1H), 2.41 (s, 3H), 2.16-2.04 (m, 1H), m 1.29 (s, 9H), 1.00 (d, \(J = 7.0\)Hz, 3H); \textsuperscript{13}C-NMR \delta 151.9, 144.3, 137.1, 129.2, 127.6, 84.8, 63.6, 49.1, 36.4, 27.7, 21.5, 14.5; MS (EI) \textsuperscript{m/z} 270 ([M-tBuO]+, 5), 184 (47), 179 (28), 155 (48), 120 (14), 108 (26), 92 (8), 91 (52), 65 (12), 58 (6), 57 (100), 56 (6); MS (EI) \textsuperscript{m/z} 363 (8), 362 (22), 361 ([M+NH\textsubscript{4}]+, 100), 305 (11). HRMS Calcd. for [M-tBuO]+ C\textsubscript{12}H\textsubscript{16}NO\textsubscript{4}S 270.0800, found 270.0787. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel AD (98% n-heptane/i-PrOH), 40°C, retention times (min): 38.6 (major) and 51.0 (minor).

\((-\rangle\rangle)-3-((tert-Butoxycarbonyl)(p-toluenesulfonyl)amino)-2-ethylpropan-1-ol (46b):

The title compound was prepared in an analogous way to 42 from 35. Purification by flash chromatography (SiO\textsubscript{2}, 50:50 Et\textsubscript{2}O/pentane, R\textsub{f} = 0.25) afforded 46b (131.0 mg) as a colorless oil. [74% yield, 90% ee, [\alpha]_D = -6.8 (c 5.8, CHCl\textsubscript{3}); \textsuperscript{1}H-NMR \delta 7.73 (d, \(J = 8.4\)Hz, 2H), 7.29 (d, \(J = 8.6\)Hz, 2H), 3.87-3.74 (m, 2H), 3.73-3.56 (m, 2H), 2.69 (bs, 1H), 2.42 (s, 3H), 1.86-1.77 (m, 1H), 1.56-1.44 (m, 1H), 1.43-1.32 (m, 1H), 1.30 (s, 9H), 0.99 (t, \(J = 7.5\)Hz, 3H); \textsuperscript{13}C-NMR \delta 152.0, 144.3, 137.0, 129.2, 127.6, 85.0, 60.3, 48.0, 42.9, 27.7, 21.6, 21.5, 11.5; MS (EI) \textsuperscript{m/z} 284 ([M-tBuO]+, 2), 216 (5), 193 (15), 184 (25), 155 (29), 120 (5), 108 (14), 92 (9), 91 (49), 65 (14), 57 (100), 56 (8), 55 (7); MS (CI) \textsuperscript{m/z} 377 (10), 376 (27), 375
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([M+NH₄]⁺, 100), 319 (47). HRMS Calcd. for [M-tBuO]⁺ C₁₃H₁₅NO₄S 284.0956, found 284.0973. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel AD (98% n-heptane/i-PrOH), 40°C, retention times (min): 35.2 (major) and 52.7 (minor).

(+)-(R)-3-(p-Toluenesulfonylamino)-1-( tert-butoxycarbonyloxy)-2-methylpropane (47):

Ozone was bubbled for 10 min through a solution of 32 (0.5 mmol) in CH₂Cl₂/MeOH (1:1,15 mL) cooled to -78°C. NaBH₄ (2.5 eq., 2.5 mmol, 95 mg) was added at -78°C after which the cooling bath was removed and the reaction mixture was stirred at rt for 2 h. The solvents were removed from the reaction mixture by rotavap (waterbath at 60 °C), followed by addition of aq. HCl (1M, 15 mL) and Et₂O (25 mL). The organic layer was separated and the resulting aqueous layer extracted with Et₂O (2x 25 mL), the combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (SiO₂, 30:70 Et₂O/pentane, Rf = 0.30) afforded 47 (123.8 mg) as a colorless oil. [69% yield, 95% ee, [α]D = + 0.6 (c 7.9, CHCl₃)]; ¹H-NMR δ 7.74 (d, J = 8.2Hz, 2H), 7.29 (d, J = 8.2Hz, 2H), 5.22 (t, J = 6.6Hz, 1H), 4.00 (dd, J = 4.7 and 11.2Hz, 1H), 3.88 (dd, J = 6.7 and 11.2Hz, 1H), 2.95-2.79 (m, 2H), 2.41 (s, 3H), 2.06-1.90 (m, 1H), 1.44 (s, 9H), 0.93 (d, J = 6.9Hz, 3H); ¹³C-NMR δ 153.6, 143.2, 136.9, 126.9, 82.2, 68.8, 45.6, 33.2, 27.6, 21.4, 14.4; MS (EI) m/z 226 (25), 225 (6), 224 (23), 199 (7), 197 (8), 188 (9), 185 (9), 184 (88), 157 (6), 156 (9), 155 (100), 133 (8), 132 (25), 119 (6), 92 (12), 91 (80), 70 (73), 65 (17), 59 (6), 57 (71), 56 (12); MS (CI) m/z 363 (7), 362 (19), 361 ([M+NH₄]⁺, 100), 333 (14), 305 (6), 289 (14). HRMS Calcd. for [M-tBuO]⁺ C₁₃H₁₆NO₄S 270.0800, found 270.0795. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel AS-H (90% n-heptane/i-PrOH), 40°C, retention times (min): 40.3 (minor) and 43.0 (major).

(−)-(R)-3-((tert-Butoxycarbonyl)(p-toluenesulfonyl)amino)-2-methylpropionic acid (48):

The title compound was prepared in an analogous way to 43 from 32. The product 48 (140.9 mg) was obtained as a white crystalline solid. [79% yield,
95% ee, $[\alpha]_D = -9.5$ (c 3.6, CHCl₃), mp = 114.4-116.3 °C; $^1$H-NMR δ 10.27 (bs, 1H), 7.80 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.6$ Hz, 2H), 4.14 (dd, $J = 6.8$ and 14.5 Hz, 1H), 3.96 (dd, $J = 7.7$ and 14.5 Hz, 1H), 3.10-3.01 (m, 1H), 2.44 (s, 3H), 1.33 (s, 9H), 1.29 (d, $J = 7.2$ Hz, 3H); $^{13}$C-NMR δ 180.5, 150.9, 144.3, 137.0, 129.2, 127.9, 84.7, 48.7, 39.7, 27.7, 21.6, 14.5; MS (EI) m/z 284 ([M-\textit{t-BuO}]$^+$, 4), 194 (5), 193 (44), 185 (5), 184 (54), 156 (5), 155 (55), 120 (18), 112 (7), 108 (34), 102 (11), 92 (7), 91 (57), 65 (14), 57 (100), 56 (7); MS (CI) m/z 377 (8), 376 (19), 375 ([M+\textit{NH}_4]^+, 100), 319 (16), 275 (6), 174 (7). HRMS Calcd. for [M-\textit{t-BuO}]$^+$ C₁₂H₁₄NO₅S 284.0592, found 284.0607. Enantiomeric excess determined on derivatized product 49.

$(-)-(R)$-Methyl 3-((\textit{tert}-butoxycarbonyl)(\textit{p}-toluenesulfonyl)amino)-2-methylpropionate (49):

To a solution of 48 (0.19 mmol, 65 mg) and MeOH (1mL) in toluene (3mL), TMSCHN$_2$ (1.0 mmol, 1.0M in Et$_2$O, 0.5 mL) was added. The reaction mixture was stirred at rt for 1 h, then MeOH (2mL) was added and the excess TMSCHN$_2$ was destroyed through addition of AcOH (0.5 mL). The mixture was diluted with toluene (5mL) and washed with sat. aq. NaHCO$_3$ (5 mL, 2x). The organic layer was dried (MgSO$_4$) and concentrated \textit{in vacuo} to yield 49 (63.6 mg) as a colorless oil, which crystallised upon standing. [94% yield, 95% ee, $[\alpha]_D = -20.8$ (c 2.8, CHCl$_3$), mp = 75.8-78.6 °C]; $^1$H-NMR δ 7.77 (d, $J = 8.2$ Hz, 2H), 7.28 (d, $J = 8.3$ Hz, 2H), 4.08 (dd, $J = 7.3$ and 14.4 Hz, 1H), 3.89 (dd, $J = 7.2$ and 14.4 Hz, 1H), 3.65 (s, 3H), 3.04-2.94 (m, 1H), 2.41 (s, 3H), 1.30 (s, 9H), 1.22 (d, $J = 7.1$ Hz, 3H); $^{13}$C-NMR δ 174.6, 150.9, 144.2, 137.2, 129.2, 127.8, 84.4, 51.8, 49.1, 39.8, 27.7, 21.5, 14.6; MS (EI) m/z 298 ([M-\textit{t-BuO}]$^+$, 4), 284 (12), 208 (7), 207 (56), 185 (6), 184 (56), 160 (7), 156 (5), 155 (59), 120 (17), 116 (29), 112 (8), 108 (32), 92 (7), 91 (54), 88 (9), 84 (6), 65 (12), 57 (100), 56 (7); MS (CI) m/z 391 (7), 390 (20), 389 ([M+\textit{NH}_4]^+, 100), 333 (13), 289 (6). HRMS Calcd. for [M-\textit{t-BuO}]$^+$ C₁₃H₁₆NO₅S 298.0749, found 298.0733. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel AD (99% \textit{n}-heptane/i-PrOH), 40°C, retention times (min): 26.9 (major) and 35.2 (minor).
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(−)-(R)-Methyl 3-tert-butoxycarbonylamino-2-methyl-propionate (50):\(^{40b}\)

The title compound was prepared in an analogous way to 44 (0.104 mmol, 38.8 mg). Work-up afforded compound 50 (20.5 mg) as a colorless oil. [90% yield, 95% ee, [α]_D = −21.8 (c 1.9, CHCl_3)]; lit.\(^{40b}\) [α]_D = −17.6 (c 2.74, CHCl_3)); \(^1\)H-NMR 4.94 (bs, 1H), 3.68 (s, 3H), 3.35-3.19 (m, 2H), 2.72-2.61 (m, 1H), 1.41 (s, 9H), 1.15 (d, J = 7.2 Hz, 3H); \(^{13}\)C-NMR \(\delta\) 175.8, 155.9, 79.3, 51.8, 42.9, 39.9, 28.3, 14.7; MS (EI) \(m/z\) 217 (M⁺, 1), 161 (29), 160 (8), 144 (19), 130 (30), 116 (6), 112 (20), 101 (7), 88 (24), 84 (8), 59 (17), 58 (6), 57 (100), 56 (8); MS (CI) \(m/z\) 452 ([2M+NH₄]+, 10), 236 (12), 235 ([M+NH₄]+, 100), 219 (6), 218 ([M+H]+, 45), 179 (16), 162 (11), 69 (9); HRMS Calcd. for \(\text{C}_{10}\text{H}_{19}\text{NO}_{4}\) \(217.1314\), found 217.1327. Enantiomeric excess determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), isothermic 130 °C, retention times (min): 13.3 (major) and 14.6 (minor).

\[ \begin{align*}
\text{Scheme 3.15: Derivatisations performed to establish the enantiomeric excess of allylic alkylation product 33. Reagents and conditions: i) 1. O₃, DCM/MeOH, -78°C, 2. NaBH₄ (5 equiv), rt, 77%; ii) BnOC(NH)CCl₃, TfOH, cyclohexane, CCl₄, rt, 25%; iii) TBAF, THF, rt.}
\end{align*} \]

(−)-(S)-3-(tert-Butyl-diphenyl-silanyloxy)-2-methylpropan-1-ol (51):\(^{49}\)

The title compound was prepared in an analogous way to 42 (0.29 mmol, 93.1 mg). Purification by flash column chromatography (SiO₂, 15:85 Et₂O/pentane, Rᵣ = 0.20) afforded 51.
(73.0 mg) as a colorless oil. [77% yield, 94% ee, $[\alpha]_D = -6.0$ (c 1.5, CHCl$_3$)]; lit.$^{49}$ $[\alpha]_D = -5.3$ (c 3.3, CHCl$_3$); $^1$H-NMR $\delta$ 7.71 (dd, J = 1.6 and 7.8 Hz, 4H), 7.49-7.39 (m, 6H), 3.77-3.59 (m, 4H), 2.68 (bs, 1H), 2.07-1.96 (m, 1H), 1.09 (s, 9H), 0.86 (d, J = 6.9 Hz, 3H); $^{13}$C-NMR $\delta$ 135.5, 135.5, 133.1, 133.1, 129.7, 127.7, 68.6, 67.5, 37.3, 26.8, 19.1, 13.1; MS (EI) $m/z$ 272 (7), 271 ([M-tBu]$^+$, 30), 229 (8), 201 (5), 200 (19), 199 (100), 197 (7), 193 (18), 181 (9), 139 (20), 77 (7); MS (CI) $m/z$ 348 (8), 347 (28), 346 ([M+NH$_4$]$^+$, 100), 330 (13), 329 ([M+H]$^+$, 47), 69 (14). HRMS Calcd. for [M-tBu]$^+$ C$_{16}$H$_{18}$O$_2$Si 271.1154, found 271.1149. Enantiomeric excess determined on derivatized product 42.

(S)-1-Benzylxoy-3-(t-butyl-diphenyl-silanyloxy)-2-methylpropane (52):

To a solution of 51 (0.15 mmol, 49.8 mg), benzyltrichloroacetimidate (0.3 mmol, 56 $\mu$L) and cyclohexane (0.3 mmol, 33 $\mu$L) in CCl$_4$ (1 mL) a catalytic amount of TfOH (2 $\mu$L) was added. The mixture was stirred at rt for 2.5 h and quenched with 1 mL sat. aq. NaHCO$_3$, after which 10 mL Et$_2$O was added and the resulting solution washed with 10 mL H$_2$O and 10 mL sat. aq. NaCl. The organic layer was dried with MgSO$_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO$_2$, 1:99 Et$_2$O/pentane, $R_f = 0.20$) afforded an inseparable mixture of 52 and the byproduct dibenzylether$^{50}$ (32.4 mg) as a colorless oil. [52:Bn$_2$O = 4:3, 25% calc. yield of 52, 94% ee]; $^1$H-NMR $\delta$ 7.69-7.64 (m, 4H), 7.45-7.26 (m, 11H + Bn$_2$O, 10H), 4.58 (Bn$_2$O, s, 4H), 4.50 (s, 2H), 3.68-3.61 (m, 2H), 3.56 (dd, J = 6.4 and 9.0 Hz, 1H), 3.40 (dd, J = 6.1 and 9.0 Hz, 1H), 2.09-1.97 (m, 1H), 1.06 (s, 9H), 0.99 (d, J = 6.9 Hz, 3H); $^{13}$C-NMR $\delta$ 138.8, 138.3 (Bn$_2$O), 135.6, 133.9, 129.5, 128.4 (Bn$_2$O), 128.3, 127.8 (Bn$_2$O), 127.6 (Bn$_2$O), 127.6, 127.5, 127.3, 73.0, 72.5, 72.1 (Bn$_2$O), 65.7, 36.3, 26.9, 19.3, 14.1; MS (EI) $m/z$ 199 (8), 195 (7), 194 (18), 193 ([M - Ph, tBu, Bn]$^+$, 100), 181 (6), 91 (50); MS (CI) $m/z$ 438 (13), 437 (35), 436 ([M+NH$_4$]$^+$, 100), 419 ([M+H]$^+$, 14). HRMS Calcd. for [M - Ph, tBu, Bn]$^+$ C$_{16}$H$_{18}$O$_2$Si 193.0685, found 193.0676. Enantiomeric excess determined for derivatized product 42. To the mixture of 52 and dibenzylether (approx. 37 $\mu$mol 52, 21 mg) 4 equivalents of TBAF (0.15 mmol, 1.0M in THF, 0.15 mL) were added at room temperature. After stirring for 2.5 h, the reaction mixture was diluted with Et$_2$O/pentane (1:1,
1mL) and the resulting mixture was flushed over a MgSO₄ and SiO₂ plug. The solution was concentrated providing the mixture of 42 and Bn₂O as an oil. The enantiomeric excess of 42 was determined to be 94% by chiral HPLC analysis, Chiralcel AS (98.5% n-heptane/i-PrOH), 40°C, retention times (min): 4.7 (Bn₂O), 11.8 (major) and 14.1 (minor).
Synthesis of chiral bifunctional building blocks through asymmetric allylic alkylation

References:


4 Similar substrates were also used by Hoveyda and coworkers in a Cu-free allylic alkylation: Lee, Y.; Hoveyda, A. H. J. Am. Chem. Soc. 2006, 128, 15604-15605.


Although Beilstein and SciFinder will not provide this result, the reaction can be found as a table footnote in: Hiyama, T.; Wakasa, N. Tetrahedron Lett. 1985, 26, 3259-3262.


Derivatization of the products was necessary, because separation of the enantiomers was not found on chiral GC or HPLC, see Experimental Part.


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46 The optical rotation in CHCl₃ is reported only once, but appears to be reported with the wrong sign. See reference 21.


50 The identity of the byproduct was established through comparison of ¹H-NMR and ¹³C-NMR spectroscopy and GCMS-data with a commercial sample. 52 was characterised as a mixture of compounds.