Chemo and enantioselective addition of grignard reagents to ketones and enolizable ketimines
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Chapter 7:
Copper-Catalyzed Enantioselective Alkylation of Enolizable Ketimines with Organomagnesium Reagents

Part of this chapter has been published:
7.1. Introduction

α-Chiral amines are important building blocks in organic synthesis and abundantly present motives in biologically active compounds.[1] Arguably, one of the most straightforward procedures to access these valuable molecules is through the addition of organometallic reagents to imines.[2] Among the different approaches to synthesize highly valuable enantioenriched amines, a chiral auxiliary strategy using Ellman’s tert-butylsulfinimines in combination with organometallics is often the method of choice.[3] On the other hand, catalytic asymmetric methods are highly attractive since only a small quantity of precious chiral ligand is needed. In this context, the first catalytic asymmetric addition of non-stabilized organometallics to aldimes via Lewis base activation, reported by Soai et al.,[4a] and a few years later Lewis acid activated copper-catalyzed organozinc additions to aldimes by Tomioka et al. were important steps.[4b] These initial reports triggered intensive research efforts in this area and a number of successful catalytic asymmetric methodologies for the addition to aldimes were developed as a result (Scheme 1, a).[4c-f,2a,b,d,f] In contrast, the progress in the catalytic asymmetric addition of organometallics to ketimines leading to α-tertiary chiral amines has been much slower and still remains a challenge due to the poorer electrophilicity of the ketimines and the more difficult enantiodiscrimination between the two substituents on the prochiral azomethine carbon (Scheme 1, b).[2b,ce] These difficulties are especially marked for acyclic ketimines, and therefore the few examples of arylation, alkynylation and allylation that have been reported to date.[5] Furthermore, the reactivity and selectivity issues described above are particularly challenging for alkylation: being less reactive good conversions are more difficult to achieve and the reagents bear the risk of β-hydride elimination, thus leading to reduction of the ketimine (Scheme 1, c). Consequently, it is not surprising that alkylation of acyclic ketimines is even now restricted to methylation and ethylation of a small set of activated ketimines (Scheme 1, d).[6]
**Scheme 1.** Asymmetric addition of organometallic reagents to acyclic ketimines. M = metal. L* = Chiral ligand. EWG = Electron withdrawing group.

Since the lower electrophilicity of ketimines is one of the major problems for this type of chemistry, the use of strong nucleophiles could be advantageous. Highly reactive organomagnesium (Grignard) reagents, which are the most commonly used organometallics both in the laboratory and in industry, would be ideal for tackling the low reactivity of the ketimines. However, so far, Grignard reagents have only been used in combination with chiral ketimines derived from Ellman’s auxiliary. This is not surprising, as the uncatalyzed addition of the Grignard reagent is a formidable competitor. Furthermore, the higher nucleophilicity goes hand in hand with increased basicity, which can cause deprotonation and thus enamide formation when enolizable ketimines are used (Scheme 1, c). Consequently, catalytic asymmetric additions of Grignard reagents to enolizable ketimines have remained elusive.
Over the past few years, our group has pursued the synthesis of chiral molecules by Cu-catalyzed asymmetric alkylation of carbonyls (See introduction and chapter 2).[9a-b] We wonder if this catalytic system would still be competent for the alkylation of enolizable imines not bearing EWG (Scheme 1, e). Although to an outsider of this chemistry it might seem as an extension of the work, merely changing the substrate, that is far from the truth. Our attempt to perform the asymmetric alkylation of diarylimines proves so (see Chapter 5).[9c] The electronic and sterics of ketimines are considerably different from ketones and thus their behavior.

7.2. Results and discussion

Initially, as is custom, we started from our previously developed work on the addition to diarylimines (see chapter 5). In this case we were unable to perform the reaction enantioselectively. Taking into account the difficulties encountered in the asymmetric addition to diarylketones (see chapter 2) compared with the success of the addition to aryl alky ketones we decided to investigate the addition to imines derived from aryl alkyl ketones. Thus, acetophenone derived imine 1a bearing diphenylphosphinyl protecting group was synthesized and subjected to the addition of hexylmagnesium bromide in the presence of a catalytic system derived from CuBr·SMe₂ salt and diphosphine ferrocenyl ligand L1 (Figure 1) at -60 °C.[10] The chemoselectivity of the reaction was poor and analysis of the crude reaction mixture by NMR revealed a complex mixture of products and ketimine 1a (entry 1). The starting material (1a) remained either due to incomplete conversion or competing enolization. The crude reaction mixture also contained reduction product, the result of yet another competing reaction via the Meerwein–Ponndorf–Verley reduction of the ketimine.[9c] We were able to increase the selectivity towards the addition product by using a Lewis acid mixture composed of BF₃·OEt₂ and CeCl₃[9a] (entry 2). However, the enantioselectivity was low and any further optimizations with this substrate were not successful. This result, together with the ease of hydrolysis of diphenylphosphinyl imines, led us to explore sulphonyl-protecting groups. To our surprise, the synthesis of 1b, several times reported with a wide variety of catalysts, repeatedly failed till the point of questioning oneself his skills as a synthetic chemist. Fortunately, microwave synthesis came in the right time and we were able to obtain not only the acetophenone derived imine, but also many others (see chapter 6). With the imine in hand, we were pleased to see that...
moderate conversion and encouraging enantiodiscrimination were obtained in the addition of HexMgBr to acetophenone-derived tosyl ketimine 1b (entry 3). To our regret, extensive screening (Figure 1) did not reveal superior ligands.

![Diagram of chiral ligands](image)

**Figure 1.** Chiral ligands screened in this project.

Nevertheless, we found that ligand L11 gave comparable results to L1, but, interestingly, with better chemoselectivity since side reduction product formation was reduced (entry 4). Therefore, further optimization studies were carried out with ligand L11. To evaluate the effect of the steric in the protecting group we tested different sulphonyl protecting groups. Using the smaller ketimine 1c with a Ms-group, instead of ketimine 1b with a Ts-group, provided the addition product 2c with lower enantiomeric excess (entry 5). On the other hand, ketimine 1d with a 2,4,6-trimethylphenyl sulphonyl protecting group underwent the addition reaction with slightly higher enantioselectivity, but lower conversion. Surprisingly, using ketimine 1e with a bulkier tert-butyl sulphonyl (Bus) group yielded an increase of the conversion towards the addition product to 89% (entry 7). At this stage L1 was evaluated again and to our delight it showed a very promising chiral induction of 59% ee (entry 8). However, the conversion towards the addition product was only
42%. Importantly, increasing the reaction temperature had a positive effect and at -50 °C the conversion raised to 71% (entry 9). The last reaction parameter studied was the solvent. This revealed that diethyl ether works better in this system than βBuOMe, but that a mixture of both is the optimal reaction medium (entries 10-11).

At this stage some chiral ligands from Walphos and Josiphos family were screened again, but none gave better results than L1. We envision that tuning the sterics or electronics of L1 would have an impact on the enantioselectivity and hoping that this would be positive we synthesized ligands showing comparable activity to L1. Regrettably, they did not show comparable activity to L1.

Table 1. Optimization of reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>L⁺</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>1:2:3 (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>L1</td>
<td>-60</td>
<td>Toluene</td>
<td>Mixture</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>L1</td>
<td>-60</td>
<td>Toluene</td>
<td>16:78:6</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>L1</td>
<td>-78</td>
<td>tBuOMe</td>
<td>41:59:0</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>L11</td>
<td>-78</td>
<td>tBuOMe</td>
<td>26:74:0</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>L11</td>
<td>-78</td>
<td>tBuOMe</td>
<td>20:70:10</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>L11</td>
<td>-78</td>
<td>tBuOMe</td>
<td>73:27:0</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>1e</td>
<td>L11</td>
<td>-78</td>
<td>tBuOMe</td>
<td>11:89:0</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>1e</td>
<td>L1</td>
<td>-78</td>
<td>tBuOMe</td>
<td>58:42:0</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>1e</td>
<td>L1</td>
<td>-50</td>
<td>tBuOMe</td>
<td>29:71:0</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>1e</td>
<td>L1</td>
<td>-50</td>
<td>Et₂O</td>
<td>21:79:0</td>
<td>66</td>
</tr>
<tr>
<td>11</td>
<td>1e</td>
<td>L1</td>
<td>-50</td>
<td>Et₂O/tBuOMe</td>
<td>17:83:0</td>
<td>74</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: conc. [1] = 0.1 M, reaction time 16-20 h (0.1 mmol). [b] Estimated by 1H NMR. [c] Determined by chiral HPLC. [d] Additives (BF₃·OEt₂/CeCl₃, 1 equiv. of each) were used.
We reasoned that the higher ee observed for \textit{Bus} compared with Ts protecting group had to come from the bigger steric hindrance generated by the first. Intrigued by the effect of relocating the bulk we prepared the analogous imine of 1b (Ts protected) but with \textit{tert}-butyl instead of methyl as alkyl substituent in the imine. Surprisingly, the bulk here proved to be too high and no conversion at all was observed. The optimized reaction conditions were applied to a wide range of aryl alkyl ketimines, and we were elated that the procedure proved to be robust, giving excellent results in most of the cases (Figure 3).\textsuperscript{[13]} We first analyzed the effect of the alkyl chain in the imine. Unexpectedly, the introduction of just one more carbon atom led to increased reactivity and full conversion, yielding 90% of addition product 5a. Even more surprisingly, the ee reached 90%. This result was further improved with ketimine 4b, which bears a propyl chain. The corresponding amine 5b was isolated in quantitative yield and with excellent 97% ee. This unusual enhancement of the reactivity when increasing the number of aliphatic carbons in the molecule shows an interesting similarity to the results obtained when changing from ketimine 1b to 1e. In either case the effect can be attributed to the increased solubility of both the substrate and corresponding reaction intermediates formed with the chiral Cu-catalyst.\textsuperscript{[12]} Thus, the increased solubility might be important when comparing the reaction rates between the catalyzed reaction and the non-catalyzed background reaction. Moreover, since both occur in the same reaction conditions, the solubility can also affect the enantioselectivity of the reaction. Giving further credence to the trend in the reactivity, product 5c with a butyl chain was obtained with quantitative yield and 91% ee.

\textit{α}-Branched imines could not be synthesized because the corresponding enamide was formed instead. Nevertheless, \textit{β}-branched imine 4d could be prepared and proved to behave similarly to the ketimines with linear counterparts. On the other hand, when cyclic 1-tetralone derived imine was subjected to the reaction conditions no addition took place. Finally, the configuration of ketimine 4c was determined, first by 1D NOE experiments, followed by definitive proof obtained from single-crystal X-ray diffraction (Figure 2).\textsuperscript{[13]} The configuration was shown to be \textit{E}, and although this was somewhat expected, there are no literature reports on the configuration of sulfonyl imines, which had been commonly assigned to be \textit{E} based on the analogy with sulfonyl aldimines. Furthermore, is interesting to note, that although \textit{E}, \textit{tert}-butyl group is pointing toward the aromatic ring, contrary to how is usually drawn in paper.
Next we studied the effect of substitution in the aromatic ring of the ketimines. Both electron-rich and electron-deficient substituents are tolerated by this catalytic system. Using ketimine 4e with the weakly electron-donating methyl in para position did not pose a problem for the reaction and the corresponding addition product 5e was isolated in excellent yield (96%) and enantioselectivity (95% ee). Ketimine 4f, with the strongly electron-donating methoxy group, was tolerated as well, although some erosion in enantioselectivity took place (5f, 84% ee). In the case of bromine-substituted ketimine the respective product 5g was isolated in quantitative yield and 94% ee. Similarly, the reaction conditions were also amenable for the strong electron-withdrawing CF<sub>3</sub> group (products 5h and 5i). Steric effects were evaluated next. As shown in the previous examples, the para position could be functionalized efficiently, and the same holds true for the meta position: the corresponding meta-substituted product 5j was obtained once again in excellent yield and ee. The ortho position could also be substituted by a fluorine, and the corresponding product 5k was obtained in 98% yield and 96% ee. A further increase in steric by replacing the fluorine in the ortho position with a methyl group pose a problem and the corresponding ketimine underwent only 15% conversion. We were particularly interested in performing this reaction with functionalized ketimines that would be amenable to further transformations after the Grignard addition. These highly reactive organometallics are often incompatible with reactive functional groups, but, remarkably, the chemoselectivity was excellent in this case. We were able to perform the addition reactions to imines containing vinyl, ester and cyano moieties in the ring, giving rise to the corresponding products 5l-n in very good yields and excellent enantioselectivities.
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Figure 3. Ketimine scope. Reaction conditions: [1a], [4a-r] = 0.1 M, 16-20 h. Isolated yields are reported. Enantiomeric excess was determined by chiral HPLC.
Furthermore, S-, O- and N-containing heteroaromatic ketimines 4o, 4p and 4q were also found to be highly suitable substrates for this asymmetric transformation, providing the corresponding addition products 5o-5q with high yields and enantioselectivities. Finally, we also demonstrated that the aromatic ring is not essential for the system and that addition to vinyl ketimines is feasible, as exemplified by product 5r, albeit with lower 61% ee and yield. If the vinyl did not have a phenyl substituent but a methyl, there was no conversion at all. The tosylated version of 5r was also subjected to the reaction conditions but the ee dropped to 18%. Contrary to the case of aryl alkyl ketones, extending the alkyl chain from methyl to propyl did not help here and not only the ee did not increase, but the selectivity worsened and a messy crude was obtained. What is clear is that a π-system does seem to be necessary for the addition to take place, as addition to dialkyl ketimines was unsuccessful. We were not very hopeful in the possibility of succeeding using diarylketones as substrates after our previous experience (Chapter 5). On the other hand, we had shown that addition to aryl heteroaryl ketones was possible (Chapter 2). Thus, the best substrate in the last case, 2-benzoylthiophene, was converted into the sulfonyl imine and tested under the standard reaction conditions. Regrettably, there was no conversion to the addition product.

To determine the absolute configuration, addition of n-butylmagnesium bromide to imine 1e was carried out (Scheme 2). The same compound was prepared by another route. Sulfinamide S1, for which the absolute configuration is known to be S,[14] was synthesized following a reported procedure.[14] Then it was oxidized with m-CPBA to yield S2. Comparison of HPLC traces revealed that the opposite enantiomer was obtained, and thus, the product obtained by our procedure was assigned to be R. The absolute configuration of other compounds was assigned by analogy.

\[
\text{CuBr-L1 complex (5 mol %)} \quad \text{BuOMe/Et}_2\text{O, -50 °C, 16 h} \quad \text{BuMgBr (2 equiv.)}
\]

\[
\begin{align*}
\text{(R) configuration} & \quad \text{HN} & \quad \text{N} & \quad \text{SO}_2 \\
\text{5y} & \quad \text{iBu} & \quad & \text{(S) configuration} \\

\text{1e} & \quad & & \text{5y} \\

\text{S2} & \quad & & \text{S1}
\end{align*}
\]

\text{Scheme 2. Determination of the absolute configuration. m-CPBA = meta-Chloroperoxybenzoic acid.}
Having established the substrate scope, we moved to the Grignard reagent scope. It was gratifying that, whereas previous reports on additions to ketimines were restricted to methylation and ethylation, our catalytic system enables the addition of a wider variety of alkyl Grignard reagents. Our methodology allows the introduction of Grignard reagents of various chain lengths, such as Et, Hex and iPent, with quantitative yields and excellent enantioselectivities (Table 2, entries 1, 2 and 4). Methylmagnesium bromide, unfortunately, gave racemic addition product. The increase in the steric hindrance caused by branching poses a problem for the reaction and α-branched Grignard reagents give almost racemic product while β-branched Grignard reagent adds with low enantioselectivity (entry 3).

Table 2. Grignard scope.

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Product</th>
<th>RMgBr</th>
<th>Yield (%)[b]</th>
<th>ee (%)[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5b</td>
<td>MeMgBr</td>
<td>Quant.</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>5s</td>
<td>EtMgBr</td>
<td>Quant.</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>5t</td>
<td>iPentMgBr</td>
<td>92</td>
<td>28</td>
</tr>
<tr>
<td>4[d]</td>
<td>5u</td>
<td>4pMgBr</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>5v</td>
<td>IsopropylMgBr</td>
<td>Quant.</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>5w</td>
<td>ChloromethylMgBr</td>
<td>36[e]</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>5x</td>
<td>BenzylMgBr</td>
<td>81</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: conc. [4b] = 0.1 M, 16-20 h. [b] Isolated yields are reported. [c] Enantiomeric excess was determined by chiral HPLC. [d] Reaction carried out at -78 °C. [e] The low yield is due to impurities present in the Grignard reagent.

Functionalized Grignard reagents, a handle for future transformations, can be introduced with excellent enantioselectivities, as demonstrated by entries 5 and 6. Finally, phenylethylmagnesium bromide was added smoothly, yielding the product...
nearly enantiopure (>99% ee, entry 7). Although alkylation and not arylation was the goal of this project we could not resist trying how the addition of phenylmagnesium bromide would go. As anticipated, probably due to its higher reactivity, racemic product was obtained.

The robustness of the methodology was further evaluated. The reaction for the synthesis of 5b was scaled up fortyfold (4 mmol), without changes in the reaction outcome (99% yield, 96% ee). The Cu-ligand complex could be recovered in 91% yield and used in a subsequent reaction, which gave the product in quantitative yield and 95% ee. Finally, the catalyst loading could be reduced from 5 mol % to 1 mol % without compromising the yield and incurring only a small decrease in the enantioselectivity (93% ee).

The final obvious step was the deprotection of the Bus group to afford the free amines. To our great regret we did not manage to do it, even if we tried all the reported procedures for removal of Bus and Tosyl protecting group. This alone would contain enough material for a separate chapter, but for the sake of space only representative examples will be discussed. The reported methods can be classified according to the deprotection conditions: 1) acidic conditions, for example, HCl in dioxane,[15a] TiOH alone or together with anisole in DCM,[15b] AlCl3 together with anisole in DCM,[15c] and H2SO4 98%[15d] all led to either starting material and/or products derived from the formation of a very stable carbocation: Friedel-Crafts reaction if anisole was present and elimination product if not; 2) basic conditions of KOH in THF/H2O mixture[15e] left the substrate untouched; 3) Reductive conditions, such as lithium in liquid ammonia,[15f] sodium naphthalene,[15g] magnesium powder in anisole in DCM,[15c] and H2SO4 98%[15d] all led to either starting material and/or products derived from the formation of a very stable carbocation: Friedel-Crafts reaction if anisole was present and elimination product if not.

Together with acyclic ketimines discussed so far, during this project cyclic ketimines were also explored as a substrate, with the hope that their fixed conformation anticipated to be crucial, as the solubility of the imine plays a key role in both the optimization is required. Together with ligand screening, solvent screening is

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Fortunately, Tosyl protected amines could be deprotected under reductive conditions (lithium in liquid ammonia). Although these amines are obtained in lower ee than the Bus protected ones, it makes the methodology suitable for obtaining enantioenriched free α-tertiary amines (Scheme 3).
Together with acyclic ketimines discussed so far, during this project cyclic ketimines were also explored as a substrate, with the hope that their fixed conformation would help the enantiodiscrimination. Several reaction conditions were tested for the addition of hexylmagnesium bromide to cyclic ketime c1 (Table 3). Carrying out the reaction at -78 °C, in tBuOMe, and with rev-Josiphos L1 as ligand low conversion and low ee was observed (Table 3, entry 1). Although L1 was the best ligand for the addition to acyclic N-sulfonyl ketimines its performance was not optimal in this case, with ligand L3 performing better (Table 3, entry 2). The best result was obtained with Walphos type ligand L11, which improved the ee to 33% (Table 3, entry 3). The low solubility of the substrate in tBuOMe is an issue, and to some extent, the low conversion can be attributed to it. In fact, changing the solvent to DCM, which solubilized the substrate yielded the product in almost full conversion, albeit in lower ee (Table 3, entry 4). Raising the temperature had also a positive effect on the conversion, but again came with an associated loss in enantioselectivity (Table 3, entry 5). Finally, we applied the optimized condition for the addition to acyclic imines (Table 3, entry 6). The change of solvent had a great impact in the solubility of the imine, and the conversion was almost full. Unfortunately, the product was racemic. From these preliminary results is clear that the catalytic asymmetric alkylation of cyclic, enolizable N-sulfonyl ketimines using Grignard reagent is feasible. Only finding the suitable reaction conditions through optimization is required. Together with ligand screening, solvent screening is anticipated to be crucial, as the solubility of the imine plays a key role in both the enantioselectivity and the conversion.

Scheme 3. Deprotection of tosylated amines.
In summary, we have developed the first asymmetric addition of Grignard reagents to enolizable ketimines. The high reactivity of Grignard reagents has been exploited to tackle the low reactivity of the ketimines. Remarkably, all competing reaction pathways, including substrate enolization, substrate reduction via β-hydride transfer, and non-catalyzed addition (commonly observed with Grignard reagents), could be avoided thanks to a highly chemoselective chiral copper/diphosphine catalyst system.

7.4. Experimental section
7.4.1. General information

All reactions using oxygen- and/or moisture-sensitive materials were carried out with anhydrous solvents under nitrogen atmosphere using oven-dried glassware and standard Schlenk techniques. Dry solvents were collected from a dry solvent
purification system. Reagents and substrates were purchased from commercial sources and used as received. EtMgBr (3 M in EtO), iBuMgBr (2 M in EtO) nHexMgBr (2 M in EtO) and iPenMgBr (2 M in EtO) were purchased from Sigma Aldrich. All the other Grignard reagents were prepared from corresponding alkyl bromides and Mg in EtO. Chiral diphosphine ligands were purchased from Sigma Aldrich and Solvias. Microwave reactions were performed with a CEM Discover SP W/Activent Unit (CEM Corp., Matthews, NC) with a continuous focused microwave power delivery system in a pressure glass vessel (10 mL) closed with an Activent™ cap under magnetic stirring. Reactions were temperature controlled, for which the MW unit adjusted the power used (maximum 250 W, average 20 W). The temperature of the reaction mixture was monitored using a calibrated infrared temperature control under the reaction vessel, and the pressure was controlled with Activent™ pressure control system.

Purification of the products was performed by filtration or by column chromatography using Merck 60 Å 230-400 mesh silica gel. Components were visualized by UV light and phosphomolybdic acid staining (phosphomolybdic acid 30 g, ethanol 1000 mL). NMR data was collected on a Varian VXR-300 (1H at 300 MHz; 13C at 50 MHz) or a Varian VXR-400 (1H at 400 MHz; 13C at 101 MHz; 19F at 376 MHz) equipped with a 5 mm z-gradient broadband probe. Chemical shifts are reported in parts per million (ppm) relative to residual solvent peak (CDCl3, 1H: 7.26 ppm; 13C: 77.16 ppm). Coupling constants are reported in Hertz (Hz). Multiplicity is reported with the usual abbreviations (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, quint: quintet, sex: sextet, m: multiplet). Exact mass spectra were recorded on a LTQ Orbitrap XL apparatus with ESI. Melting points were determined using a Büchi capillary Melting Point B-545. Enantiomeric excess (ee) were determined by chiral HPLC analysis using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector.

7.4.2. Preparation of CuBr-L1 complex

In an oven-dried Schleck 61.7 mg (1 equiv.) of CuBr-SMe2 and 187.3 mg (1.05 equiv.) of Rev-Josiphos (SL-J004-1) were dissolved in dry DCM, stirred for 15 min and the solvent was evaporated in vacuo. The analytical data were found to be in accordance with those previously reported.[16] It was stored at room temperature for several months without observing decomposition.
7.4.3. Cu-catalyzed asymmetric addition of alkyl Grignard reagents to enolizable ketimines

A flame-dried Schlenk tube equipped with septum and stirring bar was charged with 3.7 mg of CuBr-L1 complex (0.005 mmol, 0.05 equiv.), and dry tBuOMe (0.5 mL) was added. The solution was stirred under nitrogen at room temperature for 5 min. The imine (0.1 mmol, 1 equiv.) was added next: dissolved in dry Et2O (0.5 mL) if it was an oil or as a powder if it was solid. In this last case dry Et2O (0.5 mL) was added next. The solution was then cooled down to -50 °C and stirred for 5 minutes. In a separate Schlenk tube, the corresponding Grignard reagent (0.2 mmol, 2 M in Et2O) was diluted with Et2O (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture during 2 hours using a syringe pump. Once the addition was complete, the mixture was stirred for 16-20 h at –50 °C. The reaction was quenched with MeOH (0.5 mL), allowed to warm up and aqueous NH4Cl (3 mL) and Et2O (2 mL) were added, the phases separated and aqueous phase was extracted with Et2O (3x5 mL). The combined organic phases were dried with MgSO4 and concentrated under reduced pressure. In the case of products with full conversion, the compound was filtered through a pad of silica in a Pasteur pipette using a mixture of pentane:Et2O, which allowed the elution of the pure product while the catalyst remained on the silica. For compounds not reaching full conversion column chromatography was done, for which the prior hydrolysis of the remaining imine is helpful (by 1 mL of 1 M HCl to the quenched mixture). The column was done using SiO2 and mixtures of pentane:Et2O. Racemic products were synthesized following the same procedure described above but without using the CuBr-L1 complex. Dropwise addition of Grignard reagents by-hand instead of slow addition is possible in this case.

4-methyl-N-(2-phenyloctan-2-yl)benzenesulfonamide (2b)

The reaction was performed with 0.1 mmol 1b, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 2b was obtained as a colorless oil after column chromatography (SiO2, pentane:Et2O 10:1) [60% yield, 24% ee].
1H NMR (CDCl3, 400 MHz): δ 7.55 (d, J = 8.3 Hz, 2H), 7.25 – 7.11 (m, 7H), 4.79 (s, 1H), 2.38 (s, 3H), 1.91 – 1.78 (m, 2H), 1.64 (s, 3H), 1.26 – 1.15 (m, 8H), 0.83 (t, J = 7.0 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 144.1, 142.7, 140.1, 129.4, 128.2, 127.1, 127.0, 126.0, 61.9, 43.5, 31.7, 29.5, 25.8, 24.0, 22.7, 21.6, 14.2. HRMS (ESI+, m/z): calc. for 382.18112 [M+Na]+, found 382.18087. HPLC: Chiracel-ODH, n-heptane/iPrOH 97:3, 0.5 /min, 40 °C, detection at 230 nm. Retention time (min): 28.3 (major) and 41.4 (minor).

(R)-2-methyl-N-(2-phenyloctan-2-yl)propane-2-sulfonamide (2e)

The reaction was performed with 0.1 mmol 1e, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 2e was obtained as a pale yellow oil after column chromatography (SiO2, pentane:Et2O 5:1) [71% yield, 74% ee].

(R)-2-methyl-N-(3-phenylnonan-3-yl)propane-2-sulfonamide (5a)

The reaction was performed with 0.1 mmol 4a, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5a was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:Et2O 4:1) [90% yield, 90% ee].
mL/min, 40 °C, detection at 206 nm. Retention time (min): 10.5 (major) and 11.1 (minor).

(R)-2-methyl-N-(4-phenyldecan-4-yl)propane-2-sulfonamide (5b)

The reaction was performed with 0.1 mmol 4b, nHexMgBr (0.2 mmol, 2 M in Et₂O) diluted with Et₂O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et₂O. Product 5b was obtained as a pale yellow oil after filtration through a pad of silica (SiO₂, pentane:Et₂O 4:1) [quantitative yield, 97% ee].

^1H NMR (CDCl₃, 400 MHz): δ 7.43 (d, J = 7.0 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 3.5 Hz, 1H), 3.91 (s, 1H), 2.26 – 2.18 (m, 2H), 2.13 – 2.03 (m, 2H), 1.43 (s, 9H), 1.31 – 1.44, 1.42. HRMS (ESI+, m/z): calc. for 376.22807 [M+Na]^+, found 376.22758. HPLC: Chiracel-ODH, n-heptane/iPrOH 95:5, 0.5 mL/min, 40 °C, detection at 207 nm. Retention time (min): 7.7 (minor) and 8.2 (major).

(R)-2-methyl-N-(4-phenyldecan-4-yl)propane-2-sulfonamide (5b), reaction with 1 mmol % of CuBr-L1 complex:

The reaction was performed using the described procedure (vide supra) with 0.3 mmol of 4b, 1 mol % of CuBr-L1 complex, 1.5 mL of tBuOMe, 1.5 mL of Et₂O, 300 µL of nHexMgBr (2 M in Et₂O) diluted in 2.7 mL of Et₂O. Conversion was full and product 5b was isolated as above. [quantitative yield, 93% ee].

(R)-2-methyl-N-(4-phenyldecan-4-yl)propane-2-sulfonamide (5b), 4 mmol scale reaction:

The reaction was performed using the described procedure (vide supra) with 4 mmol of 4b, 5 mol % of CuBr-L1 complex, 20 mL of tBuOMe, 20 mL of Et₂O, 4 mL of nHexMgBr (2 M in Et₂O) diluted in 36 mL of Et₂O. Conversion was full and product 5b was isolated after column chromatography (SiO₂, pentane:Et₂O 10:1). [99% yield, 96% ee]. CuBr-L1 complex was isolated in 91% yield as orange solid after column chromatography (SiO₂, pentane:Et₂O 1:1).
(R)-2-methyl-N-(4-phenyldecan-4-yl)propane-2-sulfonamide (5b), reaction with recovered catalyst:

The reaction was performed using the described procedure (vide supra) with 0.1 mmol 4b, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex recovered from 1 mmol scale experiment (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Conversion was full and product 5b was isolated as above. [quantitative yield, 95% ee].

(R)-2-methyl-N-(5-phenylundecan-5-yl)propane-2-sulfonamide (5c)

The reaction was performed with 0.1 mmol 4c, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5c was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:Et2O 4:1) [quantitative yield, 91% ee].

(S)-2-methyl-N-(2-methyl-4-phenyldecan-4-yl)propane-2-sulfonamide (5d)

The reaction was performed with 0.1 mmol 4d, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5d was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:Et2O 4:1) [quantitative yield, 97% ee].
(R)-2-methyl-N-(4-(p-tolyl)decan-4-yl)propane-2-sulfonamide (5e)

The reaction was performed with 0.1 mmol 4e, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5e was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:Et2O 4:1) [96% yield, 95% ee].

1H NMR (CDCl3, 400 MHz): δ 7.27 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 3.85 (s, 1H), 2.33 (s, 3H), 2.21 – 2.13 (m, 2H), 2.07 – 1.97 (m, 2H), 1.40 (s, 9H), 1.29 – 1.16 (m, 10H), 0.88 (t, J = 7.3 Hz, 3H), 0.83 (t, J = 6.9 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 141.1, 136.7, 129.0, 126.4, 66.7, 60.4, 41.1, 38.8, 31.9, 29.7, 24.6, 24.0, 22.8, 21.1, 17.4, 14.4, 14.2. HRMS (ESI+, m/z): calc. for 390.24372 [M+Na]+, found 390.24267. HPLC: Chiracel-ODH, n-heptane/iPrOH 99:1, 0.5 mL/min, 40 °C, detection at 200 nm. Retention time (min): 12.2 (minor) and 12.9 (major).

(R)-N-(4-(4-methoxyphenyl)decan-4-yl)-2-methylpropane-2-sulfonamide (5f)

The reaction was performed with 0.1 mmol 4f, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5f was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:Et2O 4:1) [quantitative yield, 84% ee].

1H NMR (CDCl3, 400 MHz): δ 7.32 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.83 (s, 1H), 3.80 (s, 3H), 2.21 – 2.13 (m, 2H), 2.05 – 1.95 (m, 2H), 1.38 (s, 9H), 1.27-1.15 (m, 10H), 0.89 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 6.7 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 158.5, 136.1, 127.7, 113.5, 66.3, 60.4, 55.3, 40.9, 38.7, 31.9, 29.7, 24.6, 24.0, 22.8, 17.4, 14.4, 14.2. HRMS (ESI+, m/z): calc. for 406.23864 [M+Na]+, found 406.23818. HPLC:
Chiracel-ODH, n-heptane/iPrOH 99:1, 0.5 mL/min, 40 °C, detection at 228 nm. Retention time (min): 21.3 (minor) and 22.6 (major).

(R)-N-(4-(4-bromophenyl)decan-4-yl)-2-methylpropane-2-sulfonamide (5g)

The reaction was performed with 0.1 mmol 4g, nHexMgBr (0.2 mmol, 2 M in EtO) diluted with EtO (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of EtO. Product 5g was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:Et2O 4:1) [quantitative yield, 94% ee].

1H NMR (CDCl3, 400 MHz): δ 7.46 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 3.82 (s, 1H), 2.18 – 2.11 (m, 2H), 2.03 – 1.94 (m, 2H), 1.37 (s, 9H), 1.28 – 1.05 (m, 10H), 0.90 (t, J = 7.3 Hz, 3H), 0.84 (t, J = 6.6 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 143.3, 131.3, 128.5, 121.1, 65.9, 60.5, 40.5, 38.3, 31.8, 29.6, 24.5, 23.8, 22.7, 17.2, 14.4, 14.2. HRMS (ESI+, m/z): calc. for 454.13258/456.13654 [M+Na]+, found 454.13738/456.13495. HPLC: Chiracel-ODH, n-heptane/iPrOH 99.5:0.5, 0.5 mL/min, 40 °C, detection at 219 nm. Retention time (min): 32.0 (minor) and 33.3 (major).

(R)-2-methyl-N-(4-(4-(trifluoromethyl)phenyl)decan-4-yl)propane-2-sulfonamide (5h)

The reaction was performed with 0.1 mmol 4h, nHexMgBr (0.2 mmol, 2 M in EtO) diluted with EtO (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of EtO. Product 5h was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:EtO 4:1) [92% yield, 93% ee].

1H NMR (CDCl3, 400 MHz): δ 7.60 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 3.87 (s, 1H), 2.22 – 2.14 (m, 2H), 2.08 – 1.99 (m, 2H), 1.38 (s, 9H), 1.32 – 1.07 (m, 10H), 0.91 (t, J = 7.3 Hz, 3H), 0.85 (t, J = 6.6 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 148.4, 129.4, (q, J = 32.4 Hz), 127.1, 125.2 (q, J = 3.7 Hz), 124.2 (q, J = 271.9 Hz), 66.0, 60.6, 40.5, 38.4, 31.8, 29.6, 24.5, 23.7, 22.7, 17.1, 14.4, 14.1. 19F NMR (CDCl3, 376 MHz): δ -62.5. HRMS (ESI+, m/z): calc. for 444.21546 [M+Na]+, found 444.21438. HPLC: Chiracel-ODH, n-
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heptane/iPrOH 99:1, 0.5 mL/min, 20 °C, detection at 201 nm. Retention time (min): 14.1 (major) and 14.7 (minor). It was not possible to get baseline separation and therefore the reaction was performed with the other enantiomer of the catalyst (SL-J004-2) too to confirm the ee.

(R)-N-(4-(3,5-bis(trifluoromethyl)phenyl)decan-4-yl)-2-methylpropane-2-sulfonamide (5i)

The reaction was performed with 0.1 mmol 4i, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5i was obtained as a colorless oil after filtration through a pad of silica (SiO2, pentane:EtOAc 10:1) [quant. yield, 82% ee].

1H NMR (CDCl3, 400 MHz): δ 7.92 (s, 2H), 7.77 (s, 1H), 3.92 (s, 1H), 2.22 – 2.14 (m, 2H), 2.04 – 1.94 (m, 2H), 1.34 (s, 9H), 1.24 – 1.10 (m, 10H), 0.93 (t, J = 6.6 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 149.8, 133.8 (q, J = 3.1 Hz), 123.9 (d, J = 7.3 Hz, 3H), 67.4, 63.0, 42.4, 40.4, 34.2, 31.9, 26.8, 25.8, 25.2, 19.3, 16.8, 16.6. 19F NMR (CDCl3, 376 MHz): δ -62.8. HRMS (ESI+, m/z): calc. for 512.20284 [M+Na]+, found 512.19666. HPLC: Chiracel-ODH, n-heptane/iPrOH 97:3, 0.5 mL/min, 40 °C, detection at 203 nm. Retention time (min): 12.6 (minor) and 13.4 (major).

(R)-N-(4-(2-fluorophenyl)decan-4-yl)-2-methylpropane-2-sulfonamide (5k)

The reaction was performed with 0.1 mmol 4j, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5k was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:EtOAc 20:1) [92% yield, 96% ee].

1H NMR (CDCl3, 400 MHz): δ 7.35 (td, J = 8.2, 1.7 Hz, 1H), 7.31 – 7.21 (m, 1H), 7.11 – 7.07 (m, 2H), 4.06 (s, 1H), 2.23 – 2.08 (m, 2H), 1.40 (s, 9H), 1.32 – 1.14 (m, 10H), 0.90 (t, J = 6.6 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 146.5, 134.2, 129.3, 127.0, 127.0, 66.0, 60.5, 40.5, 38.4, 31.8, 29.6, 24.5, 23.7, 22.7, 17.2, 14.4, 14.2. HRMS (ESI+, m/z): calc. for 410.18910 [M+Na]+, found 410.28855. HPLC: Chiracel-ADH, n-heptane/iPrOH 98:2, 0.5 mL/min, 40 °C, detection at 208 nm. Retention time (min): 7.5 (major) and 8.5 (minor).

(R)-N-(4-(3-vinylphenyl)decan-4-yl)propane-2-sulfonamide (5l)

The reaction was performed with 0.1 mmol 4j, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5j was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:EtOAc 4:1) [93% yield, 96% ee].

1H NMR (CDCl3, 400 MHz): δ 7.40 (s, 1H), 7.33 – 7.20 (m, 3H), 3.85 (s, 1H), 2.18 – 2.10 (m, 2H), 2.04 – 1.95 (m, 2H), 1.38 (s, 9H), 1.31 – 1.06 (m, 10H), 0.91 (t, J = 7.3 Hz, 3H), 0.87 – 0.81 (t, J = 6.5 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 146.5, 134.2, 129.4, 127.3,
127.0, 124.9, 66.0, 60.5, 40.5, 38.4, 31.8, 29.6, 24.5, 23.7, 22.7, 17.2, 14.4, 14.2. HRMS (ESI+, m/z): calc. for 410.18910 [M+Na]+, found 410.28855. HPLC: Chiracel-ODH, n-heptane/iPrOH 99:1, 0.5 mL/min, 40 °C, detection at 203 nm. Retention time (min): 12.6 (minor) and 13.4 (major).

(R)-N-(4-(2-fluorophenyl)decan-4-yl)-2-methylpropane-2-sulfonamide (5k)

The reaction was performed with 0.1 mmol 4k, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with EtO (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of EtO. Product 5k was obtained as an pale yellow oil after filtration through a pad of silica (SiO2, pentane:EtO 4:1) [98% yield, 96% ee].

1H NMR (CDCl3, 400 MHz): δ 7.35 (td, J = 8.2, 1.7 Hz, 1H), 7.31 – 7.21 (m, 1H), 7.11 (td, J = 7.6, 1.4 Hz, 1H), 7.04 (ddd, J = 13.3, 8.1, 1.3 Hz, 1H), 4.06 (s, 1H), 2.24 – 2.08 (m, 4H), 1.34 (s, 9H), 1.25-1.10 (m, 10H), 0.93 (t, J = 7.3 Hz, 3H), 0.85 (t, J = 6.8 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 161.3 (d, J = 247.8 Hz), 131.1 (d, J = 9.3 Hz), 128.9 (d, J = 4.2 Hz), 123.9 (d, J = 3.3 Hz), 116.7 (d, J = 24.5 Hz), 64.6 (d, J = 2.6 Hz), 60.5, 38.5 (d, J = 3.1 Hz), 36.5 (d, J = 3.3 Hz), 31.8, 29.6, 24.3, 23.8, 22.8, 17.2, 14.4, 14.2. 19F NMR (CDCl3, 376 MHz): δ -109.2. HRMS (ESI+, m/z): calc. for 394.21865 [M+Na]+, found 394.21812. HPLC: Chiracel-ADH, n-heptane/iPrOH 98:2, 0.5 mL/min, 40 °C, detection at 207 nm. Retention time (min): 12.6 (minor) and 13.4 (major).

(R)-2-methyl-N-(4-(3-vinylphenyl)decan-4-yl)propane-2-sulfonamide (5l)

The reaction was performed with 0.1 mmol 4l, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with EtO (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of EtO. Product 5l was obtained as a colorless oil after column chromatography (SiO2, pentane:EtOAc 20:1) [92% yield, 96% ee].

1H NMR (CDCl3, 400 MHz): δ 7.43 (s, 1H), 7.37 – 7.26 (m, 3H), 6.72 (dd, J = 17.6, 10.9 Hz, 1H), 5.74 (d, J = 17.5 Hz, 1H), 5.33 – 5.23 (m, 1H), 3.89 (s, 1H), 2.23 – 2.15 (m, 2H), 2.10 – 2.00 (m, 2H), 1.40 (s, 9H), 1.31 – 1.14 (m, 10H), 0.90 (t, J = 7.3 Hz, 3H), 0.84 (t, J
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\[ J = 7.3 \text{ Hz}, 3\text{H} \].\(^{13}C\) NMR (CDCl\(_3\), 75 MHz): \( \delta 144.3, 137.4, 137.0, 128.3, 125.9, 124.7, 124.5, 113.9, 66.5, 60.3, 40.8, 38.5, 31.7, 29.5, 24.4, 23.8, 22.6, 17.2, 14.3, 14.0\). HRMS (ESI+, \( m/z \)): calc. for 402.24372 [M+Na]\(^+\), found 402.23927. HPLC: \( n \)-heptane/iPrOH 97:3, 0.5 mL/min, 40 °C, detection at 212 nm. Retention time (min): 9.7 (minor) and 12.9 (major).

**ethyl (R)-3-(4-((1,1-dimethylethyl)sulfonamido)decan-4-yl)benzoate (5m)**

![ethyl (R)-3-(4-((1,1-dimethylethyl)sulfonamido)decan-4-yl)benzoate (5m)](image)

The reaction was performed with 0.1 mmol 4m, \( n \)HexMgBr (0.2 mmol, 2 M in Et\(_2\)O) diluted with Et\(_2\)O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of \( t \)BuOMe and 0.5 mL of Et\(_2\)O. Product 5m was obtained as a colorless oil after column chromatography (SiO\(_2\), pentane:EtOAc 20:1) [82% yield, 95% ee].

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta 8.14 (s, 1\text{H}), 7.93 (d, J = 7.6 \text{ Hz}, 1\text{H}), 7.61 (d, J = 8.4 \text{ Hz}, 1\text{H}), 7.42 (t, J = 7.8 \text{ Hz}, 1\text{H}), 4.38 (q, J = 7.1 \text{ Hz}, 2\text{H}), 3.88 (s, 1\text{H}), 2.23 – 2.16 (m, 2\text{H}), 2.09 – 2.00 (m, 2\text{H}), 1.39 (t, J = 7.0 \text{ Hz}, 3\text{H}), 1.38 (s, 9\text{H}), 1.31 – 1.09 (m, 10\text{H}), 0.91 (t, J = 7.3 \text{ Hz}, 3\text{H}), 0.84 (t, J = 6.6 \text{ Hz}, 3\text{H}).\(^{13}C\) NMR (CDCl\(_3\), 100 MHz): \( \delta 149.7, 126.5, 110.4, 108.1, 62.5, 60.6, 38.5, 36.4, 31.8, 29.5, 24.1, 22.8, 19.5, 17.5, 16.8, 16.6\). HRMS (ESI+, \( m/z \)): calc. for 448.24920 [M+Na]\(^+\), found 448.24407. HPLC: Chiracel-ODH, \( n \)-heptane/iPrOH 92:8, 0.5 mL/min, 40 °C, detection at 230 nm. Retention time (min): 8.4 (minor) and 9.0 (major).

\( (R)\)-N-(4-(3-cyanophenyl)decan-4-yl)-2-methylpropane-2-sulfonamide (5n)

![\( (R)\)-N-(4-(3-cyanophenyl)decan-4-yl)-2-methylpropane-2-sulfonamide (5n)](image)

The reaction was performed with 0.1 mmol 4n, \( n \)HexMgBr (0.2 mmol, 2 M in Et\(_2\)O) diluted with Et\(_2\)O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of \( t \)BuOMe and 0.5 mL of Et\(_2\)O. Product 5n was obtained as a colorless oil after column chromatography (SiO\(_2\), pentane:EtOAc 7:1) [91% yield, 90% ee].

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta 7.73 (s, 1\text{H}), 7.71 (d, J = 8.7 \text{ Hz}, 1\text{H}), 7.55 (d, J = 7.7 \text{ Hz}, 1\text{H}), 7.45 (t, J = 7.8 \text{ Hz}, 1\text{H}), 3.88 (s, 1\text{H}), 2.19 – 2.11 (m, 2\text{H}), 2.02 – 1.94 (m, 2\text{H}), 1.34
(R)-2-methyl-N-(4-thiophen-2-yl)decan-4-yl)propane-2-sulfonamide (5o)

The reaction was performed with 0.1 mmol 4o, nHexMgBr (0.2 mmol, 2 M in Et₂O) diluted with EtO (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of EtO. Product 5o was obtained as an pale yellow oil after filtration (SiO₂, pentane:EtO 4:1) [67% yield, 95% ee].

1H NMR (CDCl₃, 400 MHz): δ 7.22 (dd, J = 4.9, 1.4 Hz, 1H), 6.98 – 6.91 (m, 2H), 3.98 (s, 1H), 2.25 – 2.18 (m, 2H), 2.07 – 1.98 (m, 2H), 1.36 (s, 9H), 1.30 – 1.19 (m, 10H), 0.92 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 6.7 Hz, 3H). 13C NMR (CDCl₃, 100MHz): δ 149.7, 126.5, 125.0, 124.4, 65.5, 60.6, 42.2, 40.1, 31.8, 29.6, 24.4, 24.1, 22.8, 17.5, 14.3, 14.2. HRMS (ESI+, m/z): calc. for 382.18449 [M+Na]+, found 382.18435. HPLC: Chiracel-ODH, n-heptane/iPrOH 99:1, 0.5 mL/min, 40 °C, detection at 237 nm. Retention time (min): 14.4 (minor) and 16.7 (major).

(R)-N-(4-(furan-2-yl)decan-4-yl)-2-methylpropane-2-sulfonamide (5p)

The reaction was performed with 0.1 mmol 4p, nHexMgBr (0.2 mmol, 2 M in Et₂O) diluted with EtO (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of EtO. Product 5p was obtained as an pale yellow oil after filtration (SiO₂, pentane:EtO 4:1) [89% yield, 90% ee].

1H NMR (CDCl₃, 400 MHz): δ 7.34 (d, J = 1.8 Hz, 1H), 6.30 (dd, J = 3.3, 1.8 Hz, 1H), 6.26 (d, J = 3.3 Hz, 1H), 3.82 (s, 1H), 2.11 – 2.04 (m, 2H), 2.00 – 1.91 (m, 2H), 1.37 – 1.24 (m, 10H), 1.24 (s, 9H), 0.92 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 5.6 Hz, 3H). 13C NMR (CDCl₃, 101 MHz): δ 156.0, 141.1, 110.4, 108.1, 62.5, 60.6, 38.5, 36.4, 31.8, 29.5, 24.1, 23.4, 22.7, 16.8, 14.3, 14.2. HRMS (ESI+, m/z): calc. for 366.20734 [M+Na]+, found
366.20718. HPLC: Chiracel-OZH, n-heptane/iPrOH 99:1, 0.5 mL/min, 20 °C, detection at 217 nm. Retention time (min): 23.4 (major) and 24.6 (minor).

(R)-2-methyl-N-(4-(1-methyl-1H-indol-5-yl)decan-4-yl)propane-2-sulfonamide (5q)

The reaction was performed with 0.1 mmol 4q, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5q was obtained as a colorless oil after column chromatography (SiO2, pentane:Et2O 10:1) [62% yield, 83% ee].

1H NMR (CDCl3, 400 MHz): δ 7.61 (t, J = 1.3 Hz, 1H), 7.29 (d, J = 1.2 Hz, 2H), 7.06 (d, J = 3.1 Hz, 1H), 6.48 (d, J = 3.1 Hz, 1H), 3.96 (s, 1H), 3.79 (s, 3H), 2.44 – 2.20 (m, 2H), 2.20 – 2.05 (m, 2H), 1.44 (s, 9H), 1.35 – 1.15 (m, 10H), 0.89 (t, J = 7.3 Hz, 3H), 0.83 (t, J = 6.3 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 138.2, 137.6, 131.9, 130.7, 122.9, 121.3, 111.6, 103.9, 70.0, 62.9, 44.2, 41.9, 35.5, 34.4, 32.3, 27.2, 26.7, 25.3, 20.1, 17.0, 16.7. HRMS (ESI+, m/z): calc. for 407.27268 [M+H]+, found 407.27225. HPLC: Chiracel-ODH, n-heptane/iPrOH 99:1, 0.5 mL/min, 40 °C, detection at 223 nm. Retention time (min): 22.9 (minor) and 33.3 (major).

(R,E)-N-(2,3-dimethyl-1-phenylnon-1-en-3-yl)-2-methylpropane-2-sulfonamide (5r)

The reaction was performed with 0.1 mmol 4r, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5r was obtained as a pale yellow oil after column chromatography (SiO2, pentane:Et2O 10:1) [37% yield, 61% ee].

1H NMR (CDCl3, 400 MHz): δ 7.32 (t, J = 7.6 Hz, 2H), 7.27 – 7.17 (m, 3H), 6.57 (s, 1H), 3.74 (s, 1H), 1.88 (s, 3H), 1.80 – 1.77 (m, 2H), 1.67 (s, 3H), 1.42 (s, 9H), 1.30 – 1.19 (m, 8H), 0.88 (t, J = 6.1 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 141.2, 138.3, 129.2, 128.2, 126.5, 126.4, 64.9, 60.2, 40.8, 31.9, 29.7, 24.6, 24.3, 24.3, 22.8, 14.6, 14.2. HRMS (ESI+,
m/z): calc. for 388.22807 [M+Na]+, found 388.22728. HPLC: Chiracel-ODH, n-heptane/iPrOH 97:3, 0.5 mL/min, 20 °C, detection at 237 nm. Retention time (min): 15.8 (minor) and 19.3 (major).

(S)-2-methyl-N-(3-phenylhexan-3-yl)propane-2-sulfonamide (5s)

The reaction was performed with 0.1 mmol 4b, EtMgBr (0.2 mmol, 3 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5s was obtained as an pale yellow oil after filtration (SiO2, pentane:EtOAc 1:1) [quantitative yield, 91% ee].

1H NMR (CDCl3, 400 MHz): δ 7.41 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.2 Hz, 1H), 3.90 (s, 1H), 2.34 – 2.00 (m, 4H), 1.41 (s, 9H), 1.26 – 1.16 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 143.7, 128.3, 127.2, 126.6, 67.2, 60.5, 40.5, 31.3, 24.6, 17.3, 14.6, 8.6. HRMS (ESI+, m/z): calc. for 320.16547 [M+Na]+, found 320.16505. HPLC: Chiracel-ODH, n-heptane/iPrOH 97:3, 0.5 mL/min, 40 °C, detection at 208 nm. Retention time (min): 11.8 (minor) and 13.0 (major).

(R)-2-methyl-N-(2-methyl-4-phenylheptan-4-yl)propane-2-sulfonamide (5t)

The reaction was performed with 0.1 mmol 4b, iButylMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5t was obtained as a colorless oil after column chromatography (SiO2, pentane:EtOAc 15:1) [92% yield, 28% ee].

1H NMR (CDCl3, 400 MHz): δ 7.43 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.29 – 7.22 (m, 1H), 3.86 (s, 1H), 2.33 – 2.14 (m, 2H), 2.11 (dd, J =13.8, 5.4 Hz, 1H), 1.94 (dd, J =13.9, 5.5 Hz, 1H), 1.56 – 1.33 (m, 3H), 1.39 (s, 9H) 0.97 (t, J = 7.3 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H), 0.55 (d, J = 6.6 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 146.7, 130.7, 129.7, 129.2, 69.4, 63.0, 51.7, 42.1, 27.3, 27.1, 26.9, 26.7, 20.0, 16.9. HRMS (ESI+, m/z): calc. for 348.19677 [M+Na]+, found 348.19405. HPLC: Chiracel-ADH, n-heptane/iPrOH 99:2:0.8, 0.5 mL/min, 40 °C, detection at 215 nm. Retention time (min): 23.2 (minor) and 26.0 (major).
(R)-2-methyl-N-(7-methyl-4-phenyloctan-4-yl)propane-2-sulfonamide (5u)

The reaction was performed with 0.1 mmol 4b, iPentylMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5u was obtained as a colorless oil after filtration (SiO2, pentane:EtOAc 10:1) [99% yield, 93% ee]. Note: Reaction was carried out at -78 °C.

1H NMR (CDCl3, 400 MHz): δ 7.40 (d, J = 7.1 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.27 – 7.23 (m, 1H), 3.88 (s, 1H), 2.25 – 2.16 (m, 2H), 2.11 – 2.01 (m, 2H), 1.53 – 1.46 (m, 1H), 1.40 (s, 9H), 1.31 – 1.01 (m, 4H), 0.92 – 0.82 (m, 9H). 13C NMR (CDCl3, 101 MHz): δ 146.6, 130.8, 129.7, 129.1, 69.2, 63.0, 43.4, 39.2, 35.3, 31.0, 27.1, 25.3, 25.2, 19.9, 16.9. HRMS (ESI+, m/z): calc. for 362.21242 [M+Na]+, found 362.20958. HPLC: Chiracel-ODH, n-heptane/iPrOH 97:3, 0.5 mL/min, 40 °C, detection at 207 nm. Retention time (min): 8.7 (minor) and 9.6 (major).

(R)-2-methyl-N-(4-phenylnon-8-en-4-yl)propane-2-sulfonamide (5v)

The reaction was performed with 0.1 mmol 4b, pent-4-en-1-ylmagnesium bromide (0.2 mmol, 1.8 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5v was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:Et2O 4:1) [quantitative yield, 91% ee].

1H NMR (CDCl3, 400 MHz): δ 7.40 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.7 Hz, 2H), 7.25 (tt, J = 7.1, 1.4 Hz, 1H), 5.73 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.00-4.91 (m, 2H), 3.88 (s, 1H), 2.25 – 2.15 (m, 2H), 2.12-2.01 (m, 4H), 1.40 (s, 9H), 1.35-1.18 (m, 4H), 0.89 (t, J = 7.3 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 144.0, 138.6, 128.4, 127.3, 126.5, 114.9, 66.7, 60.5, 41.0, 38.3, 34.0, 24.6, 23.3, 17.4, 14.4. HRMS (ESI+, m/z): calc. for 360.19677 [M+Na]+, found 360.19651. HPLC: Chiracel-ODH, n-heptane/iPrOH 98:2, 0.5 mL/min, 40 °C, detection at 210 nm. Retention time (min): 12.0 (minor) and 12.8 (major).

(R)-N-(8-chloro-4-phenyloctan-4-yl)-2-methylpropane-2-sulfonamide (5w)

The reaction was performed with 0.1 mmol 4b, (4-chlorobutyl)magnesium bromide (0.3 mmol*, 0.9 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5w was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:Et2O 4:1) [36% yield, 95% ee]. *0.3 mmol were used because the purity of the Grignard reagent was aprox.70%.

1H NMR (CDCl3, 400 MHz): δ 7.40 – 7.34 (m, 4H), 7.28 – 7.25 (m, 1H), 3.89 (s, 1H), 3.51 – 3.45 (m, 2H), 2.29 – 2.02 (m, 4H), 1.77 (quint, J = 7.0 Hz, 2H), 1.41 (s, 9H), 1.25 – 1.19 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 143.7, 128.5, 127.4, 126.4, 66.7, 60.6, 44.9, 41.5, 37.8, 32.9, 24.6, 21.6, 17.4, 14.4. HRMS (ESI+, m/z): calc. for 382.15780 [M+Na]+, found 382.15750. HPLC: Chiracel-ODH, n-heptane/iPrOH 99:1, 0.5 mL/min, 40 °C, detection at 209 nm. Retention time (min): 17.6 (minor) and 18.4 (major).

(R)-N-(1,3-diphenylhexan-3-yl)-2-methylpropane-2-sulfonamide (5x)

The reaction was performed with 0.1 mmol 4b, PhenylethylMgBr (0.4 mmol, 2.3 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5x was obtained as a colorless oil after column chromatography (SiO2, pentane:EtOAc 15:1) [81% yield, >99% ee].

1H NMR (CDCl3, 400 MHz): δ 7.47 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.34 – 7.24 (m, 3H), 7.19 – 7.16 (m, 3H), 3.97 (s, 1H), 2.64 – 2.42 (m, 4H), 2.29 – 2.09 (m, 2H), 1.43 (s, 9H), 1.31 – 1.19 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 146.2, 144.6, 131.1, 131.0, 129.9, 128.9, 128.5, 69.2, 63.1, 44.0, 43.4, 33.0, 27.1, 25.3, 25.2, 19.9, 16.9. HRMS (ESI+, m/z): calc. for 396.19677 [M+Na]+, found 396.19623. HPLC: Chiracel-ODH, n-heptane/iPrOH 98:2, 0.5 mL/min, 40 °C, detection at 209 nm. Retention time (min): 23.7 (major) and 30.4 (minor).
(R)-N-(8-chloro-4-phenyloctan-4-yl)-2-methylpropane-2-sulfonamide (5w)

The reaction was performed with 0.1 mmol 4b, (4-chlorobutyl)magnesium bromide (0.3 mmol*, 0.9 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5w was obtained as a pale yellow oil after filtration through a pad of silica (SiO2, pentane:Et2O 4:1) [36% yield, 95% ee]. *0.3 mmol were used because the purity of the Grignard reagent was approx.70%.

1H NMR (CDCl3, 400 MHz): δ 7.40 – 7.34 (m, 4H), 7.28 – 7.25 (m, 1H), 3.89 (s, 1H), 3.51 – 3.45 (m, 2H), 2.29 – 2.02 (m, 4H), 1.77 (quint, J = 7.0 Hz, 2H), 1.41 (s, 9H), 1.25 – 1.19 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 143.7, 128.5, 127.4, 126.4, 66.7, 60.6, 44.9, 41.5, 37.8, 32.9, 24.6, 21.6, 17.4, 14.4. HRMS (ESI+, m/z): calc. for 382.15780 [M+Na]+, found 382.15750. HPLC: Chiracel-ODH, n-heptane/iPrOH 99:1, 0.5 mL/min, 40 °C, detection at 209 nm. Retention time (min): 17.6 (minor) and 18.4 (major).

(R)-N-(1,3-diphenylhexan-3-yl)-2-methylpropane-2-sulfonamide (5x)

The reaction was performed with 0.1 mmol 4b, PhenylethylMgBr (0.4 mmol, 2.3 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5x was obtained as a colorless oil after column chromatography (SiO2, pentane:EtOAc 15:1) [81% yield, >99% ee].

1H NMR (CDCl3, 400 MHz): δ 7.47 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.34 – 7.24 (m, 3H), 7.19 – 7.16 (m, 3H), 3.97 (s, 1H), 2.64 – 2.42 (m, 4H), 2.29 – 2.09 (m, 2H), 1.43 (s, 9H), 1.31 – 1.19 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 146.2, 144.6, 131.1, 131.0, 129.9, 128.9, 128.5, 69.2, 63.1, 44.0, 43.4, 33.0, 27.1, 19.9, 16.9. HRMS (ESI+, m/z): calc. for 396.19677 [M+Na]+, found 396.19623. HPLC: Chiracel-ODH, n-heptane/iPrOH 98:2, 0.5 mL/min, 40 °C, detection at 209 nm. Retention time (min): 23.7 (major) and 30.4 (minor).
Copper-Catalyzed Enantioselective Alkylation of Enolizable Ketimines with Organomagnesium Reagents

(R)-2-methyl-N-(2-phenylhexan-2-yl)propane-2-sulfonamide (5y)

The reaction was performed with 0.1 mmol 1e, n-butyilmagnesium bromide (0.2 mmol, 1.8 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5y was obtained as a pale yellow oil after column chromatography (SiO2, pentane:Et2O 5:1) [70% yield, 52% ee].

$^1$H NMR (CDCl3, 400 MHz): δ 7.45 (d, $J = 7.1$ Hz, 2H), 7.35 (t, $J = 7.7$ Hz, 2H), 7.26 (t, $J = 7.3$ Hz, 1H), 4.00 (s, 1H), 2.06 – 1.93 (m, 2H), 1.82 (s, 3H), 1.40 (s, 9H), 1.30– 1.05 (m, 4H), 0.84 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl3, 101 MHz): δ 145.9, 128.5, 127.2, 125.8, 63.2, 60.2, 43.7, 26.6, 25.9, 24.6, 23.0, 14.1. HRMS (ESI+, m/z): calc. for 320.16547 [M+Na]+, found 320.16547. HPLC: Chiracel-ODH, n-heptane/iPrOH 97:3, 0.5 mL/min, 40 °C, detection at 208 nm. Retention time (min): 13.0 (major) and 15.6 (minor).

3-hexyl-3-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (c2)

The product was isolated in variable yield (see table 3) after column chromatography (SiO2, pentane:EtOAc 5:1)

$^1$H NMR (CDCl3, 400 MHz): δ 7.75 (d, $J = 7.7$ Hz, 1H), 7.63 (td, $J = 7.6$, 1.2 Hz, 1H), 7.52 (td, $J = 7.6$, 1.1 Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 1H), 4.37 (s, 1H), 1.93 – 1.81 (m, 2H), 1.62 (s, 3H), 1.44 – 1.06 (m, 8H), 0.85 (t, $J = 6.5$ Hz, 3H). $^{13}$C NMR (CDCl3, 101 MHz): δ 145.0, 135.4, 133.4, 129.3, 123.1, 121.5, 64.1, 41.9, 31.7, 29.3, 28.6, 24.1, 22.7, 14.2. HRMS (ESI+, m/z): calc. for 268.13658[M+H]+, found 268.13688. The ee was determined by HPLC analysis (Chiracel-ODH, n-heptane/iPrOH 90:10, 0.5 mL/min). Retention time (min): 17.8 (minor) and 25.5 (major).
7.4.4. Deprotection of sulfonamide products

(R)-4-methyl-N-(2-methyl-5-phenylundecan-5-yl)benzenesulfonamide (5z-1)

The reaction was performed with 0.1 mmol 4z-1, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5z-1 was obtained as a pale yellow oil after column chromatography (SiO2, pentane:Et2O 5:1) [65% yield, 68% ee].

1H NMR (CDCl3, 400 MHz): δ 7.49 (d, J = 8.2 Hz, 2H), 7.21 - 7.19 (m, 2H), 7.13 - 7.11 (m, 5H), 4.81 (s, 1H), 2.38 (s, 3H), 2.19 - 2.12 (m, 1H), 1.94 (dd, J = 13.9, 5.4 Hz, 1H), 1.84 (dd, J = 13.9, 5.7 Hz, 1H), 1.58 - 1.45 (m, 1H), 1.26-1.11 (m, 9H), 0.84 (t, J = 7.1 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H), 0.58 (d, J = 6.7 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 142.6, 142.6, 140.0, 129.3, 128.0, 127.1, 126.9, 126.7, 65.0, 47.8, 37.2, 31.8, 29.5, 24.7, 24.3, 24.0, 23.8, 22.8, 21.6, 14.2. HRMS (ESI+, m/z): calc. for 402.24613 [M+H]+, found: 402.24533. HPLC: Chiracel-ODH column, n-heptane/iPrOH 99:1, 0.5 mL/min, 40 °C, detection at 230 nm. Retention time (min): 46.7 (minor) and 49.5 (major).

(R)-4-methyl-N-(4-phenyldecan-4-yl)benzenesulfonamide (5z-2)

The reaction was performed with 0.1 mmol 4z-2, nHexMgBr (0.2 mmol, 2 M in Et2O) diluted with Et2O (1 mL total volume), CuBr-L1 complex (3.7 mg, 0.005 mmol, 5 mol%) in 0.5 mL of tBuOMe and 0.5 mL of Et2O. Product 5z-1 was obtained as a pale yellow oil after column chromatography (SiO2, pentane:Et2O 10:1) [89% yield, 64% ee].

1H NMR (CDCl3, 400 MHz): δ 7.51 (d, J = 8.3 Hz, 2H), 7.21 - 7.12 (m, 7H), 4.74 (s, 1H), 2.38 (s, 3H), 2.01 - 1.95 (m, 2H), 1.90 - 1.82 (m, 2H), 1.20 - 0.91 (m, 10H), 0.82 (t, J = 7.1 Hz, 3H), 0.78 (t, J = 7.3 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 142.6, 142.6, 140.0, 129.3, 128.0, 127.1, 126.8, 126.5, 65.0, 40.4, 38.0, 31.8, 29.5, 23.5, 22.7, 21.6, 16.8, 14.2, 14.2. HRMS (ESI-, m/z): calc. for 386.21483 [M-H]-, found: 386.21518. HPLC: Chiracel-ODH column, n-heptane/iPrOH 97:3, 0.5 mL/min, 40 °C, detection at 243 nm. Retention times: 19.6 min (minor) and 20.7 min (major).
Copper-Catalyzed Enantioselective Alkylation of Enolizable Ketimines with Organomagnesium Reagents

(R)-2-methyl-5-phenylundecan-5-amine (6z-1)

Gaseous NH₃ was generated by reaction of NaOH and NH₄Cl, dried with CaO and condensed into a flask at −78 °C (5 mL). Lithium wire (14 mg, 2.0 mmol) was cut in small pieces and was added portionwise to the liquid NH₃. A solution of 5z-1 (27 mg, 0.067 mmol) in THF (0.5 mL) was then added and the mixture was stirred for 20 min at −78 °C. The reaction was quenched with NH₄Cl, and the flask was warmed to room temperature to evaporate off the NH₃. Then, the solution was basified with NaHCO₃ sat. sol. and extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under vacuum. Amine was obtained after column chromatography (SiO₂, Et₂O:MeOH 20:1) [62% yield, 68% ee].

1H NMR (CDCl₃, 400 MHz): δ 7.40 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 1.82–1.53 (m, 7H), 1.25–1.19 (m, 8H), 0.85 (d, J = 7.1 Hz, 3H), 0.59 (d, J = 6.6 Hz, 3H). 13C NMR (CDCl₃, 101 MHz): δ 147.6, 128.1, 125.9, 124.0 (minor) and 126.2 (major).

(R)-4-phenyldecan-4-amine (6z-2)

The same procedure described for 6z-1 was followed using 0.1 mmol of 5z-2. Amine 6z-2 was obtained after column chromatography (SiO₂, pentane:EtO 20:1→0:1). [84% yield, 64% ee].

1H NMR (CDCl₃, 400 MHz): δ 7.39 (d, J = 7.4 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 1.85–1.50 (m, 6H), 1.27–1.14 (m, 8H), 1.05–0.92 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H). 13C NMR (CDCl₃, 101 MHz): δ 147.6, 128.1, 125.9, 125.8, 58.0, 46.7, 44.2, 31.9, 30.0, 23.8, 22.8, 17.1, 14.7, 14.2. HRMS (ESI+, m/z): calc. for 234.22163 [M+H]+, found: 234.22150.
7.4.5. Synthesis of ketones

Ketones 1, 4a-d, 4f, 4o, 4p, 4s, 4u, 4v were commercially available. All the other ketones were synthesized according to a literature procedure[17]: To a solution of bis[2-(N,N,-dimethylaminoethyl)] ether (0.75 mL, 3.9 mmol) in THF (12 mL) was added n-propyl magnesium chloride (1.95 mL, 3.9 mmol, 2 M solution in Et₂O) at 0 °C. The mixture was stirred at 0 ºC for 15 min and it was added over 20 minutes to a solution of the acyl chloride (3 mmol) in THF (6 mL) at -60 ºC. After the addition it was kept stirring for an additional 5 minutes. Reaction was quenched with aq. NH₄Cl, extracted with AcOEt (3X) and the combined organic phases were dried over MgSO₄ and concentrated in vacuo. The ketone was not purified and the crude was used directly for the synthesis of the corresponding N-sulfonyl imine. In the cases where there was not full conversion the crude was washed with pentane and filtered. The solid was discarded and the liquid was concentrated in vacuo. Ketones 4e[18], 4g[19], 4h[20], 4k[21], 4l[22], 4r[24] and 4t[25] have already been reported. All new ketones have been characterized:

1-(3,5-bis(trifluoromethyl)phenyl)butan-1-one

The product was synthesized following the described procedure above and obtained as a yellow oil in quantitative yield.

¹H NMR (CDCl₃, 400 MHz): δ 8.38 (s, 2H), 8.06 (s, 1H), 3.01 (t, J = 7.2 Hz, 2H), 1.81 (sex, J = 7.4 Hz, 2H), 1.04 (t, J = 7.4 Hz, 3H). ¹³C NMR(CDCl₃, 400 MHz): δ 199.8, 141.1, 134.96 (q, J = 33.9 Hz), 130.63 (d, J = 4.0 Hz), 128.69 (hept, J = 4.1 Hz), 125.56 (q, J = 273.0 Hz), 43.24, 19.91, 16.27. ¹⁹F NMR (CDCl₃, 376 MHz): δ -63.1.

Methyl 3-butyrylbenzoate

The product was synthesized following described procedure above and obtained as a yellow oil in quantitative yield. The 3-(methoxycarbonyl)benzoyl chloride used to synthesize this ketone was synthesized from-(methoxycarbonyl)benzoic acid by treating with excess SOCl₂ for 2 h at r.t. Excess of SOCl₂ was removed under vacuum and 3-(methoxycarbonyl)benzoyl chloride was used, without further purification, for the synthesis of the ketone following the above described procedure.
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1H NMR (CDCl₃, 300 MHz) δ 8.59 (s, 1H), 8.29 – 8.11 (m, 2H), 7.55 (t, J = 7.8 Hz, 1H), 3.95 (s, 3H), 2.99 (t, J = 7.3 Hz, 2H), 1.79 (sex, J = 7.4 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H).

13C NMR (CDCl₃, 400 MHz): δ 202.0, 168.9, 139.9, 136.2, 134.7, 133.2, 131.7, 131.4, 55.0, 43.2, 20.2, 16.4. HRMS (ESI+, m/z): calc. for 207.10157 [M+H]+, found 207.09954.

3-butyrylbenzonitrile

The product was synthesized following described procedure above and obtained as a colorless oil in quantitative yield.

1H NMR (CDCl₃, 400 MHz) δ 8.23 (s, 1H), 8.17 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 2.95 (t, J = 7.2 Hz, 2H), 1.77 (sex, J = 7.3 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H).

13C NMR (CDCl₃, 400 MHz): δ 198.1, 137.7, 135.8, 131.5, 131.7, 129.6, 118.0, 113.1, 40.5, 17.4, 13.7. HRMS (ESI+, m/z): calc. for 174.09134 [M+H]+, found 174.09092.

1-(1-methyl-1H-indol-5-yl)butan-1-one

This ketone was synthesized in a different way: In a Schlenk flask 1-methyl-1H-indole-5-carbaldehyde (3.14 mmol, 1 equiv.) was added and dissolved in THF (5 mL). To this solution nPrMgCl (4.08 mmol, 1.3 equiv.) was added dropwise at 0 °C, allowed to warm to r.t. and stirred for an additional 2 hours. The alcohol product was obtained as a pale yellow oil after aqueous work up in quantitative yield and used in the next step without further purification. 1-(1-methyl-1H-indol-5-yl)butan-1-ol (3.1 mmol, 1 equiv.) obtained in the previous step was oxidized with PDC (5.75, 1.85 equiv.) in 5 mL DCM. After complete conversion silica (20 g) was added to the reaction and reaction mixture was filtered through a pad of basic alumina by washing with EtOAc. Volatiles were removed under vacuum to obtain a yellow oil (which became solid while standing at r.t.) in 51% yield.

1H NMR (CDCl₃, 400 MHz) δ 8.31 (d, J = 1.6 Hz, 1H), 7.91 (dd, J = 8.7, 1.7 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.10 (d, J = 3.1 Hz, 1H), 6.60 (dd, J = 3.1, 0.8 Hz, 1H), 3.80 (s, 3H), 3.02 (t, J = 7.4 Hz, 2H), 1.81 (q, J = 7.4 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H).

13C NMR (CDCl₃, 101 MHz): δ 203.2, 141.7, 133.0, 132.0, 130.6, 125.4, 124.4, 111.7, 105.6, 43.1, 35.6, 21.0, 16.7. HRMS (ESI+, m/z): calc. for 202.1264 [M+H]+, found 201.1266.
7.4.6. Synthesis of enolizable N-sulfonyl ketimines

Our previously reported method (see Chapter 6)[26] was followed with slight modifications. A 10 mL microwave vial equipped with a stirrer was charged, under ambient atmosphere, with the ketone (1-10 mmol), the sulfonamide (1.2 equiv.), dry toluene (0.5 M) and Ti(OEt)₄ (1.2 equiv.) The vial was closed and heated at 150 °C for 150 minutes using microwave irradiation. After completion, vial was cooled to room temperature, diluted with 5 mL of AcOEt, quenched with 1 mL of NaHCO₃, and filtered through a pad of celite. The crude product was purified by flash chromatography on silica gel using mixtures of pentane and AcOEt as the eluent. All new ketimines have been characterized:

**(E)-4-methyl-N-(1-phenylethylidene)benzenesulfonamide (1b)**

The product was isolated in 75% yield after column chromatography (SiO₂, pentane:AcOEt 10:1). The analytical data were found to be in accordance with those reported in the literature[26,27].

\[ \text{^{1}H NMR (CDCl₃, 400 MHz): } \delta 7.93 (d, J = 8.1 \text{ Hz}, 2H), 7.90 (d, J = 7.9 \text{ Hz}, 2H), 7.54 (t, J = 7.4 \text{ Hz}, 1H), 7.41 (t, J = 7.7 \text{ Hz}, 2H), 7.35 (d, J = 8.0 \text{ Hz}, 2H), 2.99 (s, 3H), 2.45 (s, 3H). \]

**N-(1-Phenylethylidene)methanesulfonamide (1c)**

The product was isolated in 37% yield after column chromatography (SiO₂, pentane:AcOEt 5:1). The analytical data were found to be in accordance with those reported in the literature[26].

\[ \text{^{1}H NMR (CDCl₃, 400 MHz): } \delta 7.92 (d, J = 7.7 \text{ Hz}, 2H), 7.55 (t, J = 7.4 \text{ Hz}, 1H), 7.44 (t, J = 7.7 \text{ Hz}, 2H), 3.22 (s, 3H), 2.88 (s, 3H). \]

**N-(1-Phenylethylidene)-2,4,6-trimethylphenylsulfonamide (1d)**

The product was isolated in 27% yield after column chromatography (SiO₂, pentane:AcOEt 5:1). The analytical data were found to be in accordance with those reported in the literature[26,28].
1H NMR (CDCl₃, 400 MHz): δ 7.91 (d, J = 7.4 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 6.98 (s, 2H), 2.95 (s, 3H), 2.69 (s, 6H) 2.32 (s, 3H).

**N-(1-Phenylethylidene)-t-butanesulfonamide (1e)**

The product was isolated in 46% yield after column chromatography (SiO₂, pentane:AcOEt 10:1). The analytical data were found to be in accordance with those reported in the literature.

1H NMR (CDCl₃, 400 MHz): δ 7.93 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 2.91 (s, 3H), 1.55 (s, 9H). 13C NMR (CDCl₃, 101 MHz): δ 180.5, 137.7, 133.0, 128.7, 128.0, 59.1, 24.0, 21.2.

**(E)-2-methyl-N-(1-phenylpropylidene)propane-2-sulfonamide (4a)**

The product was isolated in 33% yield as a white solid after column chromatography (SiO₂, pentane:AcOEt 10:1).

1H NMR (CDCl₃, 400 MHz): δ 7.93 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 2.91 (s, 3H), 1.55 (s, 9H), 1.33 (t, J = 7.7 Hz, 3H). 13C NMR (CDCl₃, 101 MHz): δ 185.5, 136.4, 133.0, 128.9, 128.5, 59.3, 27.9, 24.2, 12.9. HRMS (ESI+, m/z): calc. for 276.10287 [M+Na]+, found 276.10289. M.p.: 73-74 °C

**(E)-2-methyl-N-(1-phenylbutylidene)propane-2-sulfonamide (4b)**

The product was isolated in 51% yield as a yellow oil after column chromatography (SiO₂, pentane:AcOEt 15:1).

1H NMR (CDCl₃, 400 MHz): δ 7.89 (d, J = 7.7 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 3.29 (t, J = 7.9 Hz, 2H), 1.74 (s, 9H), 1.05 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl₃, 101 MHz): δ 184.5, 136.8, 132.9, 128.8, 128.3, 59.2, 36.5, 24.1, 22.2, 14.5. HRMS (ESI+, m/z): calc. for 290.11852 [M+Na]+, found 290.11859.
(E)-2-methyl-N-(1-phenylpentylidene)propane-2-sulfonamide (4c)

The product was isolated in 32% yield as an off-yellow oil after column chromatography (SiO₂, pentane:AcOEt 20:1).

\[ \begin{align*}
\text{N} & \quad \text{SO}_2 \\
\text{Me} & \quad \text{CH}_2 \\
\text{C}_6\text{H}_{13} & \quad \text{CH}_2 \text{CH}_2 \text{CH}_2 \\
\text{Ph} & \quad \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_3
\end{align*} \]

\[^1\text{H}\text{ NMR (CDCl}_3\text{, 400 MHz):} \delta 7.90 (d, \text{ } J = 7.2 \text{ Hz, } 2\text{H}), 7.55 (t, \text{ } J = 7.5 \text{ Hz, } 1\text{H}), 7.45 (t, \text{ } J = 7.8 \text{ Hz, } 2\text{H}), 3.32 (t, \text{ } J = 8.3 \text{ Hz, } 2\text{H}), 2.09 (m, \text{ } 2\text{H}), 1.52 (s, \text{ } 9\text{H}), 1.05 (t, \text{ } J = 7.3 \text{ Hz, } 3\text{H}). \]

\[^{13}\text{C NMR (CDCl}_3\text{, 101 MHz):} \delta 185.0, 143.9, 134.2, 129.6, 128.5, 59.2, 36.4, 24.2, 22.4, 21.7, 14.6. \]

HRMS (ESI+, \textit{m/z}): calc. for 280.13658 [M+Na\(^+=\)], found 280.13700. M.p.: 86-87 °C.

(E)-2-methyl-N-(3-methyl-1-phenylbutylidene)propane-2-sulfonamide (4d)

The product was isolated in 26% yield as a white solid after column chromatography (SiO₂, pentane:AcOEt 15:1).

\[ \begin{align*}
\text{N} & \quad \text{SO}_2 \\
\text{Me} & \quad \text{CH}_2 \\
\text{C}_6\text{H}_{13} & \quad \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_3
\end{align*} \]

\[^1\text{H}\text{ NMR (CDCl}_3\text{, 400 MHz):} \delta 7.82 (d, \text{ } J = 7.7 \text{ Hz, } 2\text{H}), 7.53 (t, \text{ } J = 7.4 \text{ Hz, } 1\text{H}), 7.43 (t, \text{ } J = 7.6 \text{ Hz, } 2\text{H}), 3.27 (d, \text{ } J = 6.7 \text{ Hz, } 6\text{H}), 1.52 (s, \text{ } 9\text{H}), 1.04 (d, \text{ } J = 6.7 \text{ Hz, } 6\text{H}). \]

\[^{13}\text{C NMR (CDCl}_3\text{, 101 MHz):} \delta 184.3, 143.9, 134.2, 129.6, 128.5, 59.2, 36.4, 24.2, 22.4, 21.7, 14.6. \]

HRMS (ESI-, \textit{m/z}): calc. for 280.13658 [M-H\(^-\)], found 280.13700. M.p.: 86-87 °C.

(E)-2-methyl-N-(1-(p-tolyl)butylidene)propane-2-sulfonamide (4e)

The product was isolated in 63% yield as a pale yellow oil after column chromatography (SiO₂, pentane:AcOEt 20:1).

\[ \begin{align*}
\text{N} & \quad \text{SO}_2 \\
\text{Me} & \quad \text{CH}_2 \\
\text{C}_6\text{H}_{13} & \quad \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_3
\end{align*} \]

\[^1\text{H}\text{ NMR (CDCl}_3\text{, 400 MHz):} \delta 7.80 (d, \text{ } J = 8.0 \text{ Hz, } 2\text{H}), 7.24 (d, \text{ } J = 8.2 \text{ Hz, } 2\text{H}), 3.27 (t, \text{ } J = 8.2 \text{ Hz, } 2\text{H}), 2.41 (s, \text{ } 3\text{H}), 1.53 (s, \text{ } 9\text{H}), 1.05 (t, \text{ } J = 7.3 \text{ Hz, } 3\text{H}). \]

\[^{13}\text{C NMR (CDCl}_3\text{, 101 MHz):} \delta 184.3, 143.9, 134.2, 129.6, 128.5, 59.2, 36.4, 24.2, 22.4, 21.7, 14.6. \]

HRMS (ESI+, \textit{m/z}): calc. for 304.13417 [M+Na\(^+=\)], found 304.13433.

(E)-N-(1-(4-methoxyphenyl)butylidene)-2-methylpropane-2-sulfonamide (4f)

The product was isolated in 29% yield as a yellow oil after column chromatography (SiO₂, pentane:AcOEt 10:1).

\[ \begin{align*}
\text{N} & \quad \text{SO}_2 \\
\text{MeO} & \quad \text{CH}_2 \\
\text{C}_6\text{H}_{13} & \quad \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_3
\end{align*} \]
Copper-Catalyzed Enantioselective Alkylation of Enolizable Ketimines with Organomagnesium Reagents

1H NMR (CDCl₃, 400 MHz): δ 7.89 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 3.86 (s, 3H), 3.24 (t, J = 8.2 Hz, 2H), 1.74 (sex, J = 7.4 Hz, 2H), 1.52 (s, 9H), 1.05 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl₃, 101 MHz): δ 183.3, 163.7, 130.6, 129.2, 114.1, 59.1, 55.6, 36.2, 24.2, 22.6, 14.6. HRMS (ESI+, m/z): calc. for 324.07955 [M+Na]⁺, found 324.07926.

(E)-N-(1-(4-bromophenyl)butylidene)-2-methylpropane-2-sulfonamide (4g)

The product was isolated in 15 % yield over two steps (starting from the acyl chloride) as a yellow oil after column chromatography (SiO₂, pentane:AcOEt 20:1).

1H NMR (CDCl₃, 400 MHz): δ 7.75 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 3.26 (t, J = 8.1 Hz, 2H), 1.71 (sex, J = 7.5 Hz, 2H), 1.53 (s, 9H), 1.04 (t, J = 7.3 Hz, 3H). 13C NMR (CDCl₃, 101 MHz): δ 183.4, 135.7, 132.2, 129.8, 128.0, 59.4, 36.4, 24.1, 22.2, 14.5. HRMS (ESI+, m/z): calc. for 368.10591 [M+H]⁺, found 368.10523.

(E)-2-methyl-N-(1-(4-(trifluoromethyl)phenyl)butylidene)propane-2-sulfonamide (4h)

The product was isolated in 29 % yield over two steps (starting from the acyl chloride) as a yellow oil after column chromatography (SiO₂, pentane:AcOEt 20:1).

1H NMR (CDCl₃, 400 MHz): δ 7.98 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 3.31 (t, J = 8.1 Hz, 2H), 1.70 (sex, J = 7.5 Hz, 2H), 1.53 (s, 9H), 1.04 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl₃, 101 MHz): δ 183.3, 140.2, 134.12 (q, J = 33.0 Hz), 128.6, 125.9 (q, J = 3.6 Hz), 123.67 (q, J = 272.6 Hz), 59.5, 36.6, 24.1, 21.9, 14.4. 19F NMR (CDCl₃, 376 MHz): δ -63.2. HRMS (ESI+, m/z): calc. for 358.10591 [M+Na]⁺, found 358.10523.

(E)-N-(1-(3,5-bis(trifluoromethyl)phenyl)butylidene)-2-methylpropane-2-sulfonamide (4i)

The product was isolated in 15% yield as a pale yellow oil after column chromatography (SiO₂, pentane:AcOEt 20:1).

1H NMR (CDCl₃, 400 MHz): δ 8.28 (s, 2H), 8.04 (s, 1H), 3.34 (t, J = 8.0 Hz, 2H), 1.72 (sex, J = 7.4 Hz, 2H), 1.54 (s, 9H), 1.07 (t, J =
7.3 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 181.5, 139.1, 132.6 (q, $J = 34.0$ Hz), 128.3 – 127.9 (m), 126.0 (hept, $J = 6.7$, 3.4 Hz), 123.0 (q, $J = 272.8$ Hz), 59.7, 36.3, 24.1, 21.8, 14.4. $^{19}$F NMR (CDCl$_3$, 376 MHz): $\delta$ -63.2. HRMS (ESI+, m/z): calc. for 404.11135 [M+H]$^+$, found 404.10707.

**[(E)-N-(1-(3-chlorophenyl)butylidene)-2-methylpropane-2-sulfonamide (4j)](image)**

The product was isolated in 31% yield over two steps (starting from the acyl chloride) as a yellow oil after column chromatography (SiO$_2$, pentane:AcOEt 20:1).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.84 (s, 1H), 7.75 (d, $J = 7.9$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 3.26 (t, $J = 8.0$ Hz, 1H), 1.72 (sex, $J = 7.5$ Hz, 2H), 1.54 (s, 9H), 1.06 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 183.2, 138.7, 135.1, 132.8, 130.2, 128.2, 126.5, 59.4, 36.5, 24.1, 22.1, 14.5. HRMS (ESI+, m/z): calc. for 324.07955 [M+Na]$^+$, found 324.07926.

**[(E)-N-(1-(2-fluorophenyl)butylidene)-2-methylpropane-2-sulfonamide (4k)](image)**

The product was isolated in 16% yield over two steps (starting from the acyl chloride) as a yellow oil after column chromatography (SiO$_2$, pentane:AcOEt 15:1). It consisted of a mixture of rotamers (78:22).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.65 - 7.09 (m, 8H, major and minor), 3.31 (t, $J = 7.9$ Hz, 2H, major), 2.75 (t, $J = 7.4$ Hz, 2H, minor), 1.72 - 1.67 (m, 2H, minor), 1.62 (sex, $J = 7.3$ Hz, 2H, major), 1.51 (s, 9H, major), 1.46 (s, 9H, minor), 0.99 (t, $J = 7.4$ Hz, 3H, minor), 0.96 (t, $J = 7.4$ Hz, 3H, major). $^{13}$C NMR (CDCl$_3$, 101 MHz, for the major isomer): $\delta$ 184.3, 162.3, 159.7, 133.6 (d, $J = 9.2$ Hz), 130.5, 124.6 (d, $J = 3.6$ Hz), 116.9 (d, $J = 23.1$ Hz), 59.4, 39.5, 39.5, 24.0, 21.1, 14.2. $^{19}$F NMR (CDCl$_3$, 376 MHz): $\delta$ -111.9 (major), -114.3 (minor). HRMS (ESI+, m/z): calc. for 286.12715 [M+H]$^+$, found 286.12786.

**[(E)-2-methyl-N-(1-(3-vinylphenyl)butylidene)propane-2-sulfonamide (4l)](image)**

The product was isolated in 27% yield as a pale yellow oil after column chromatography (SiO$_2$, pentane:AcOEt 20:1).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.87 (s, 1H), 7.76 (d, $J = 7.4$ Hz, 1H), 7.58 (d, $J = 7.7$ Hz, 1H), 7.40 (t, $J = 7.8$ Hz, 1H), 6.74 (dd, $J =$
Copper-Catalyzed Enantioselective Alkylation of Enolizable Ketimines with Organomagnesium Reagents

17.6, 10.9 Hz, 1H), 5.78 (d, J = 17.6 Hz, 1H), 5.32 (d, J = 10.9 Hz, 1H), 3.29 (t, J = 7.8 Hz, 2H), 1.73 (sex, J = 7.4 Hz, 2H), 1.53 (s, 9H), 1.04 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 184.4, 138.1, 137.1, 136.0, 130.2, 129.0, 127.5, 126.0, 115.3, 59.1, 36.4, 24.0, 22.1, 14.4. HRMS (ESI+, m/z): calc. for 294.15472 [M+H]+, found 294.14956.

**ethyl (E)-3-(1-((tert-butylsulfonyl)imino)butyl)benzoate (4m)**

The product was isolated in 36 % yield over two steps (starting from the acyl chloride) as a pale yellow oil after column chromatography (SiO2, pentane:AcOEt 20:1). Note: Transesterification from methyl benzoate to ethyl benzoate was observed during imine synthesis in presence of Ti(OEt)4.

1H NMR (CDCl3, 400 MHz): δ 8.52 (s, 1H), 8.19 (d, J = 7.7 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.31 (t, J = 8.2 Hz, 2H), 1.71 (sex, J = 7.6 Hz, 2H), 1.53 (s, 9H), 1.39 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 186.2, 168.3, 139.8, 136.0, 134.8, 133.8, 132.0, 131.6, 64.0, 61.9, 39.0, 26.7, 24.5, 17.0, 16.9. HRMS (ESI+, m/z): calc. for 340.15771 [M+H]+, found 340.15472.

**(E)-N-(1-(3-cyanophenyl)butylidene)-2-methylpropane-2-sulfonamide (4n)**

The product was isolated in 36 % yield over two steps (starting from the acyl chloride) as a pale yellow oil after column chromatography (SiO2, pentane:AcOEt 20:1).

1H NMR (CDCl3, 400 MHz): δ 8.13 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 3.30 (t, J = 8.0 Hz, 2H), 1.64 (sex, J = 7.4 Hz, 2H), 1.52 (s, 9H), 1.03 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl3, 75 MHz): δ 182.1, 137.9, 135.5, 132.2, 131.7, 129.8, 117.9, 113.4, 59.4, 36.2, 24.0, 21.8, 14.3. HRMS (ESI+, m/z): calc. for 293.13183 [M+H]+, found 293.12923.

**(E)-2-methyl-N-(1-(thiophen-2-yl)butylidene)propane-2-sulfonamide (4o)**

The product was isolated in 50% yield as a yellow oil after column chromatography (SiO2, pentane:AcOEt 10:1). It consisted of a 75:25 ratio of imine:enamide. Characterization for the imine:

1H NMR (CDCl3, 400 MHz): δ 7.65 (d, J = 3.6 Hz, 1H), 7.58 (d, J = 4.9 Hz, 3H), 7.36 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 173.3, 152.5, 147.4, 133.2, 132.0, 131.9, 130.9, 129.8, 119.6, 113.4, 105.7, 74.7, 61.6, 44.1, 35.7, 26.9, 22.0, 17.3. HRMS (ESI+, m/z): calc. for 280.09779 [M+H]+, found 280.09769.
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17.6, 10.9 Hz, 1H), 5.78 (d, J = 17.6 Hz, 1H), 5.32 (d, J = 10.9 Hz, 1H), 3.29 (t, J = 7.8 Hz, 2H), 1.73 (sex, J = 7.4 Hz, 2H), 1.53 (s, 9H), 1.04 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 184.4, 138.1, 137.1, 136.0, 130.2, 129.0, 127.5, 126.0, 115.3, 59.1, 36.4, 24.0, 22.1, 14.4. HRMS (ESI+, m/z): calc. for 294.15223 [M+H]+, found 294.14956.

**Ethyl (E)-3-(1-(tert-butylsulfonyl)imino)butyl)benzoate (4m)**

The product was isolated in 36% yield over two steps (starting from the acyl chloride) as a pale yellow oil after column chromatography (SiO2, pentane:AcOEt 20:1).

1H NMR (CDCl3, 400 MHz): δ 8.52 (s, 1H), 8.19 (d, J = 7.7 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.31 (t, J = 8.2 Hz, 2H), 1.71 (sex, J = 7.6 Hz, 2H), 1.53 (s, 9H), 1.39 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 186.2, 168.3, 139.8, 136.0, 134.8, 133.8, 132.0, 131.6, 64.0, 61.9, 39.0, 26.7, 24.5, 17.0, 16.9. HRMS (ESI+, m/z): calc. for 340.15771 [M+H]+, found 340.15472.

**2-(N-(1-(furan-2-yl)butylidene)-2-methylpropane-2-sulfonamide (4n)**

The product was isolated in 36% yield over two steps (starting from the acyl chloride) as a pale yellow oil after column chromatography (SiO2, pentane:AcOEt 20:1).

1H NMR (CDCl3, 300 MHz): δ 8.13 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 3.30 (t, J = 8.0 Hz, 2H), 1.64 (sex, J = 7.4 Hz, 2H), 1.52 (s, 9H), 1.03 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl3, 75 MHz): δ 182.1, 137.9, 135.5, 132.2, 131.7, 129.8, 117.9, 113.4, 59.4, 36.2, 24.0, 21.8, 14.3. HRMS (ESI+, m/z): calc. for 293.13183 [M+H]+, found 293.12923.

**2-(N-(1-(thiophen-2-yl)butylidene)propane-2-sulfonamide (4o)**

The product was isolated in 50% yield as a yellow oil after column chromatography (SiO2, pentane:AcOEt 10:1). It consisted of a 75:25 ratio of imine:enamide. Characterization for the imine:

1H NMR (CDCl3, 400 MHz): δ 7.65 (d, J = 3.6 Hz, 1H), 7.58 (d, J = 4.9 Hz, 1H), 7.10 (t, J = 4.3 Hz, 1H), 3.18 (t, J = 8.3 Hz, 2H), 1.83 (sex, J = 7.7 Hz, 2H), 1.48 (s, 9H), 1.06 (t, J = 7.4 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 177.8, 144.0, 134.3, 132.9, 128.5, 59.0, 36.9, 23.9, 23.0, 14.6. HRMS (ESI+, m/z): calc. for 296.17494 [M+Na]+, found 296.07497.

**2-(N-(1-(1-methyl-1H-indol-5-yl)butylidene)propane-2-sulfonamide (4q)**

The product was isolated in 35% yield as a yellow oil after column chromatography (SiO2, pentane:AcOEt 20:1). The product is not pure due to inseparable impurities.

1H NMR (CDCl3, 400 MHz): δ 8.30 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 3.2 Hz, 1H), 6.66 (d, J = 3.2 Hz, 1H), 3.80 (s, 3H), 3.44 (t, J = 8.1 Hz, 2H), 1.98 – 1.83 (m, 2H), 1.66 (s, 9H), 1.17 (t, J = 7.3 Hz, 3H). 13C NMR (CDCl3, 101 MHz): δ 187.7, 141.9, 133.2, 131.9, 130.9, 125.7, 124.6, 112.1, 105.7, 61.6, 44.1, 35.7, 26.9, 22.0, 17.3. HRMS (ESI+, m/z): calc. for 321.16313 [M+Na]+, found 321.16302.

**2-(N-((2E,3E)-3-methyl-4-phenylbut-3-enylidene)propane-2-sulfonamide (4r)**

The product was isolated in 14% yield as a pale yellow oil after column chromatography (SiO2, pentane:AcOEt 10:1).

1H NMR (CDCl3, 400 MHz): δ 7.48 (s, 1H), 7.44 – 7.31 (m, 5H), 2.77 (s, 3H), 2.09 (s, 3H), 1.51 (s, 9H). 13C NMR (CDCl3, 101
Copper-Catalyzed Enantioselective Alkylation of Enolizable Ketimines with Organomagnesium Reagents

1H NMR (CDCl3, 400 MHz): δ 8.14 (dd, J = 8.0, 1.3 Hz, 1H), 7.46 (td, J = 7.5, 1.4 Hz, 1H), 7.35 – 7.16 (m, 2H), 3.33 (t, J = 6.5 Hz, 2H), 2.90 (t, J = 6.1 Hz, 2H), 2.04 (quint, J = 6.4 Hz, 2H), 1.56 (s, 9H). 13C NMR (CDCl3, 101 MHz): δ 180.6, 144.3, 133.6, 132.3, 129.2, 127.2, 126.8, 59.2, 33.2, 29.5, 24.1. HRMS [M+Na]+ calc. for 288.10287, found 288.10302. M.p. 88.5-89.5 °C.

(E)-N-(3,4-dihydronaphthalen-1(2H)-ylidene)-2-methylpropane-2-sulfonamide

The product was isolated in 28% yield as a white solid after column chromatography (SiO2, pentane:AcOEt 15:1).

(E)-2-methyl-N-(1-(o-tolyl)butylidene)propane-2-sulfonamide

The product was isolated in 38% yield as pale yellow oil after column chromatography (SiO2, pentane:AcOEt 20:1). It consisted of a mixture of rotamers (52:48).

(E)-N-(1-cyclohexylethylidene)-2-methylpropane-2-sulfonamide

The product was isolated in 36% yield as an off-yellow oil after column chromatography (SiO2, pentane:AcOEt 10:1).
(Z)-2-methyl-N-(phenyl(thiophen-2-yl)methylene)propane-2-sulfonamide

The product was isolated in 32% yield as an off-yellow oil after column chromatography (SiO₂, pentane:AcOEt 15:1).

\[
\text{\begin{align*}
\text{SO}_2 & \text{N} \\
& \text{O} \\
& \text{C} \text{C} \text{H} \\
& \text{S} \text{H} \\
& \text{T} \text{H} \\
& \text{O} \\
& \text{N} \\
& \text{C} \text{C} \text{H} \text{C} \\
\end{align*}}
\]

\( \text{H} \text{NMR (CDCl}_3\text{, 400 MHz): } \delta 7.69 \text{ (dd, } J = 5.0, 1.2 \text{ Hz, } 1\text{H}), \delta 6.1 (d, J = 6.8 \text{ Hz, } 2\text{H}), \delta 7.55 - 7.44 \text{ (m, } 3\text{H}), \delta 7.20 (d, J = 4.0 \text{ Hz, } 1\text{H}), \delta 7.07 (t, J = 4.4 \text{ Hz, } 1\text{H}), 1.52 (s, 9\text{H}). \text{^{13}C NMR (CDCl}_3\text{, 101 MHz): } \delta 173.5, 144.4, 137.2, 135.3, 130.8, 128.6, 128.4, 127.8, 59.1, 24.0. \text{HRMS [M+Na}^+\text{calc. for 330.05929, found 330.05902.}

(E)-4-methyl-N-(3-methyl-1-phenylbutylidene)benzenesulfonamide (4z-1)

The product was isolated in 51% yield as an off-yellow oil after column chromatography (SiO₂, pentane:AcOEt 10:1).

\[
\text{\begin{align*}
\text{SO}_2 & \text{N} \\
& \text{O} \\
& \text{C} \text{C} \text{H} \\
& \text{S} \text{H} \\
& \text{T} \text{H} \\
& \text{O} \\
& \text{N} \\
& \text{C} \text{C} \text{H} \text{C} \\
\end{align*}}
\]

\( \text{H} \text{NMR (CDCl}_3\text{, 400 MHz): } \delta 7.92 (d, J = 8.2 \text{ Hz, } 2\text{H}), 7.79 (t, J = 7.1 \text{ Hz, } 2\text{H}), 7.51 (t, J = 7.4 \text{ Hz, } 1\text{H}), 7.41 (t, J = 7.7 \text{ Hz, } 2\text{H}), 7.33 (d, J = 8.2 \text{ Hz, } 2\text{H}), 3.41 - 3.33 \text{ (m, } 2\text{H}), 2.44 (s, 3\text{H}), 2.14 \text{ (septet, } J = 6.6 \text{ Hz, } 1\text{H}), 1.00 (d, J = 6.6 \text{ Hz, } 6\text{H}). \text{^{13}C NMR (CDCl}_3\text{, 101 MHz): } \delta 184.0, 143.5, 139.0, 137.4, 132.8, 129.5, 128.7, 128.6, 127.2, 42.3, 29.2, 22.7, 21.7. \text{HRMS (ESI+, } m/z): \text{calc. for 316.13658 [M+H}^+\text{], found 316.13691.}

(E)-4-methyl-N-(1-phenylbutylidene)benzenesulfonamide (4z-2)

The product was isolated in 65% yield as an off-yellow oil after column chromatography (SiO₂, pentane:AcOEt 10:1).

\[
\text{\begin{align*}
\text{SO}_2 & \text{N} \\
& \text{O} \\
& \text{C} \text{C} \text{H} \\
& \text{S} \text{H} \\
& \text{T} \text{H} \\
& \text{O} \\
& \text{N} \\
& \text{C} \text{C} \text{H} \text{C} \\
\end{align*}}
\]

\( \text{H} \text{NMR (CDCl}_3\text{, 400 MHz): } \delta 7.93 (d, J = 8.2 \text{ Hz, } 2\text{H}), 7.85 (d, J = 7.5 \text{ Hz, } 2\text{H}), 7.52 (t, J = 7.4 \text{ Hz, } 1\text{H}), 7.41 (t, J = 7.7 \text{ Hz, } 2\text{H}), 7.33 (d, J = 8.1 \text{ Hz, } 2\text{H}), 3.38 (m, 2\text{H}), 2.44 (s, 3\text{H}), 1.78 \text{ (sex, } J = 7.5 \text{ Hz, } 2\text{H}), 1.09 (t, J = 7.3 \text{ Hz, } 3\text{H}). \text{^{13}C NMR (CDCl}_3\text{, 101 MHz): } \delta 183.7, 143.5, 139.0, 136.6, 133.0, 129.5, 128.8, 128.6, 127.2, 36.3, 22.3, 21.7, 14.5. \text{HRMS (ESI+, } m/z): \text{calc. for 302.12093 [M+H}^+\text{], found: 302.12091.}
Synthesis of 3-methylbenzo[d]isothiazole 1,1-dioxide (c1)

The product was synthesized following a literature procedure[29] and isolated in 45% yield after crystallization. The analytical data were found to be in accordance with those reported in the literature.[29]

1H NMR (CDCl₃, 400 MHz): δ 7.91-7.93 (m, 1H), 7.68-7.76 (m, 3H), 2.67 (s, 3H). 13C NMR (CDCl₃, 101 MHz): δ 173.3, 139.7, 134.1, 133.7, 131.7, 124.2, 122.5, 17.7.

7.4.7. Synthesis of Cu-complexes of chiral ligands L8 and L9

(R)-1-Dicyclohexylphosphano-2-[α-(S)-(N,N-dimethylamino)ethyl]ferrocene (7)

Following the described procedure[30] sec-Butyllithium (1.4 M in cyclohexane, 1.65 mL, 2.3 mmol) was added to a solution of Ugi’s amine (420 μL, 2 mmol) in Et₂O (8 mL) at 0 °C. After 2 h, chlorodicyclohexylphosphane (530 μL, 2.4 mmol) was added at 0 °C and the solution was allowed to warm up to rt and stirred overnight. Saturated aqueous Na₂CO₃ (3 mL) was added and the layers were separated. The aqueous layer was extracted three times with CH₂Cl₂ (8 mL) and the combined organic layers were dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO₂, pentane:Et₂O 5:1) to give the compound 7 as an orange solid (0.64 g, 71%). The analytical data were found to be in accordance with those reported in the literature.[30]

1H NMR (CDCl₃, 400 MHz): δ 4.26 (d, 2H), 4.08 (s, 1H), 0.8–2.0 (m, 25H), 4.05 (s, 5H), 2.38 (s, 1H), 2.10 (s, 6H). 31P NMR (CDCl₃, 162 MHz): δ -11.3 (s).

(R)-1-[((S)-2-(Dicyclohexylphosphino)ferrocenyl)-ethyl-di(3,5-bis-(trifluoromethyl)phenyl)phosphine-Cu complex L8-CuBr

A mixture of 7 (181.4 mg, 0.4 mmol) and bis(3,5-di(trifluoromethyl)phenyl)phosphine (200 mg, 0.44 mmol) in acetic acid (6 mL) were degassed three times and stirred for 5 h at 90 °C under nitrogen atmosphere. The solvent was removed under reduced pressure and the yellow residue was dissolved in CH₂Cl₂. The organic layer was washed with saturated aqueous Na₂CO₃, brine and H₂O. The organic layer was dried on MgSO₄.
and the solvent was removed under reduced pressure. The crude product was dissolved in CH₂Cl₂ (5 mL) and CuBr·SMe₂ (84 mg, 0.4 mmol) was added. The mixture was stirred at rt for 2 h. The solvent was removed in vacuo and the product was purified by column chromatography (SiO₂, pentane:EtO 5:1) to give compound **L8-CuBr** as an orange solid in 25% yield (0.1 mmol, 101.5 mg). The analytical data were found to be in accordance with those reported in the literature.[30]

**1H NMR (CDCl₃, 400 MHz):** δ 8.29 (s, 2H), 7.90 (s, 1H), 7.87 (s, 2H), 7.37 (s, 1H), 4.33 (s, 1H), 4.22 (s, 1H), 4.20 (s, 5H), 4.13 (s, 1H), 3.87 (q, 1H), 1.1–2.0 (m, 25H).

(R)-1-[(Sorg)-2-(Dicyclohexylphosphino)ferrocenyl]-ethyl-di(3,5-xylyl)phosphine-Cu complex **L9-CuBr**

Prepared according to the procedure described for **L8-CuBr**, using 7 (170 mg, 0.37 mmol), bis(3,5-dimethylphenyl)phosphine (100 mg, 0.41 mmol) and CuBr·SMe₂ (76 mg, 0.37 mmol). Purified on column chromatography (SiO₂, pentane:EtO 5:1) to give compound **L9-CuBr** as an orange solid in 46% yield (0.17 mmol, 135.3 mg) as after column chromatography (SiO₂, pentane:EtO 5:1).

**1H NMR (CDCl₃, 400 MHz):** δ 7.33 (d, J = 9.2 Hz, 2H), 7.16 (d, J = 9.1 Hz, 2H), 6.97 (s, 1H), 6.89 (s, 1H), 4.31 (d, J = 13.5 Hz, 2H), 4.20 (s, 1H), 4.02 (s, 5H), 3.57 (m, 1H), 2.57 (m, 1H), 2.29 (s, 6H), 2.19 (s, 6H), 2.03 – 0.69 (m, 12H). **13C NMR (CDCl₃, 101 MHz):** δ 138.1 (d, J = 9.3 Hz), 137.7 (d, J = 9.6 Hz), 132.5 (dd, J = 19.0, 8.2 Hz), 132.0 (d, J = 16.2 Hz), 131.8, 131.6 (d, J = 16.4 Hz), 131.6, 130.1 (m), 128.7, 125.6, 93.6 (d, J = 24.4 Hz), 74.4 (d, J = 18.6 Hz), 73.4, 68.9, 39.4 (dd, J = 11.0, 5.7 Hz), 35.5 (m), 33.7 (d, J = 11.1 Hz), 31.8 (d, J = 10.9 Hz), 30.3 (dd, J = 14.3, 6.7 Hz), 29.8, 28.1 (d, J = 16.5 Hz), 27.3 (d, J = 8.4 Hz), 26.8 (d, J = 12.3 Hz), 26.1 (d, J = 25.5 Hz), 24.3, 21.4 (d, J = 19.8 Hz), 18.6. **3¹P NMR (CDCl₃, 162 MHz):** δ 13.5. HRMS calc. for 792.13676 [M]+, found 792.13707.
7.4.8. X-ray data

Molecular structure of compound 4c, showing 50% probability ellipsoids. Hydrogen atoms, and one of the disorder components of the butyl chain are omitted for clarity.

A single crystal of compound 4c was mounted on top of a cryoloop and transferred into the cold nitrogen stream (100 K) of a Bruker-AXS D8 Venture diffractometer. Data collection and reduction was done using the Bruker software suite APEX2.[31] The final unit cell was obtained from the xyz centroids of 9898 reflections after integration. A multiscan absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings (SADABS). The structures were solved by direct methods using SHELX.[32] and refinement of the structure was performed using SHELXL.[33] From the refinement it was clear that 3 carbon atoms of the butyl chain were disordered over two positions. This was described with two disorder components, for which the site occupancy factor of both components refined to 0.5. The carbon atoms C9A and C9B were found very close together, and ISOR instructions were applied to prevent their atomic displacement parameters becoming non-positive definite. DFIX instructions were applied to constrain the C-C bond lengths in the disordered part to chemically reasonable values. The hydrogen atoms were generated by geometrical considerations, constrained to idealised geometries and allowed to ride on their carrier atoms with an isotropic displacement parameter related to the equivalent displacement parameter of their carrier atoms. Crystal data and details on data collection and refinement are presented in Table S1.
7.4.8 X-ray data

Molecular structure of compound 4c, showing 50% probability ellipsoids. Hydrogen atoms, and one of the disorder components of the butyl chain are omitted for clarity.

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The structures were solved by direct methods using SHELXT [32] and refinement of the structure was performed using SHELXL. [33] From the refinement it was clear that 3 carbon atoms of the butyl chain were disordered over two positions. This was described with two disorder components, for which the site occupancy factor of both components refined to 0.5. The carbon atoms C9A and C9B were found very close together, and ISOR instructions were applied to prevent their atomic displacement parameters becoming non-positive definite. DFIX instructions were applied to constrain the C-C bond lengths in the disordered part to chemically reasonable values. The hydrogen atoms were generated by geometrical considerations, constrained to idealised geometries and allowed to ride on their carrier atoms with an isotropic displacement parameter related to the equivalent displacement parameter of their carrier atoms. Crystal data and details on data collection and refinement are presented in Table S1.

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<td>GooF</td>
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<td>Weighting a,b</td>
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<td>restraints</td>
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<td>min, max resid dens</td>
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7.5. References


[11] For studying the scope of the reaction with respect to ketimine substrates and Grignard reagents premade chiral copper complex (Cu-L1) was used as a catalyst.

[12] This hypothesis also correlates with the fact that the reaction mixture derived from the addition of Grignard reagents to ketimines 1b-1d is heterogeneous, when compared to those derived from additions to 4a-4d.

[13] CCDC 1509347 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.


[31] Bruker, 2012. APEX2 (v2012.4-3), SAINT (Version 8.18C) and SADABS (Version 2012/1).
Bruker AXS Inc., Madison, Wisconsin, USA
[31] Bruker, 2012. APEX2 (v2012.4-3), SAINT (Version 8.18C) and SADABS (Version 2012/1).
If we knew what it was we were doing, it would not be called research, would it?

Attributed to Albert Einstein

The most common solvents for the asymmetric catalysis using Grignard reagents are Et₂O, tBuOMe and CH₂Cl₂. While the solution structure of Grignard reagents in the former is known, that is not the case for tBuOMe and CH₂Cl₂. This chapter describes the use of 1D and 2D NMR spectroscopy to determine the structure of alkyl Grignard reagents in them. It has been found that at conditions commonly used in asymmetric catalysis (0.15-0.5 M, -78 °C) Grignard reagents in tBuOMe and CH₂Cl₂ are monomeric.