Harnessing the reactivity of alkenyl heteroarenes through copper catalysis and Lewis acids

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Chapter 4
Copper Catalysed Alkylation of β-Substituted 2- and 4-Alkenyl Pyridines

In this chapter, development of a protocol for the asymmetric alkylation of 4- and 2-alkenyl pyridines using chiral copper catalyst and Grignard reagents is presented. The reactivity of pyridine-based alkenyl substrates was harnessed using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as Lewis acid. In contrast, activated alkenyl pyridines underwent addition reactions more easily with boron based Lewis acid BF₃·OEt₂ with remarkable functional group tolerance.

Part of this chapter has been published:
4.1 Introduction

Among all the aromatic heterocycles, pyridine is one of most important due to its strong abundance in bioactive molecules such as pharmaceuticals and agrochemicals (Figure 1).\textsuperscript{1}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Examples of pyridine containing pharmaceuticals and agrochemicals.}
\end{figure}

To date, pyridines are the most commonly found nitrogen containing aromatic heterocycles among U.S. FDA approved pharmaceuticals\textsuperscript{2} and they are present in more than 60 currently marketed drugs. Pyridines are also relevant scaffolds in chemical processes, since they are often employed as additives or ligands.\textsuperscript{3} Their immense importance pushed the research towards the development of new and efficient synthetic strategies to access different pyridine derivatives, making it an important challenge in the field of organic chemistry for decades.\textsuperscript{4} The most commonly used and straightforward approach is the direct functionalization of the pyridine ring, even though introduction of stereogenic centre with this method would require the use of super stoichiometric amount of chiral reagents. In the last decade, the exploitation of the pyridine ring to activate an adjacent olefin towards conjugate addition of carbon nucleophiles has emerged as a more elegant tool.\textsuperscript{5} Common Michael acceptors are activated by an electron withdrawing group via both inductive effect and resonance. In comparison, pyridine can be considered as a weak electron withdrawing group since it activates the conjugated double bond in alkenyl pyridine only by resonance, making them poorly electrophilic substrates. In this context, the substitution of the olefin moiety has a significant impact on the reactivity. While non-enantioselective conjugate additions to unsubstituted vinyl pyridines are well known in literature\textsuperscript{6} (Scheme 1a), examples of general methodologies for enantioselective additions to β-substituted alkenyl pyridines are rare.\textsuperscript{7} To overcome the intrinsic low reactivity of these substrates, the few reported methodologies rely on the use of electron poor pyridines, higher temperature, and rare metal catalysts (Scheme 1b).\textsuperscript{5b,7}
Despite the efficiency of these methodologies in delivering the corresponding conjugate addition products, the nucleophiles scope is quite narrow and to the best of our knowledge introduction of aliphatic chains is not yet developed. In this chapter, the development of a methodology for the alkylation of alkenyl pyridines will be discussed.

**4.2 Result and Discussion**

As already mentioned in the previous chapter (Chapter 2, page 30), Lewis acid activation using BF$_3$·OEt$_2$ or other boron additives proved to be insufficient to promote the conjugated addition of Grignard reagents to alkenyl pyridines (Table 1, entries 1, 2, 3). We hypothesised that a tighter interaction between the LA and the pyridine substrate could guarantee a stronger activation. While in the reaction between pyridine and BF$_3$·OEt$_2$ most likely a Lewis acid-base couple will be generated, formation of an actual covalent bond should result in the formation of cationic species that could exhibit higher reactivity. To test this hypothesis, 4-styryl pyridine 1a was subjected to conjugate addition of EtMgBr in presence of copper complex of chiral dihosphine ligand using TMSOTf instead of BF$_3$·OEt$_2$. This change promoted only moderately the formation of the corresponding addition product 2a (50% conversion) although with high enantioselectivity (85% ee) (Table 1, entry 4).
**Table 1: Lewis acids optimization.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Lewis acid</th>
<th>Equiv.</th>
<th>Conv. (%)[^b]</th>
<th>ee (%)[^c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^d]</td>
<td>Et₂O</td>
<td>BF₃·Et₂O</td>
<td>1.1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2[^d]</td>
<td>DCM</td>
<td>BF₃·Et₂O</td>
<td>1.1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3[^d]</td>
<td>DCM</td>
<td>BF₃·PhF₅</td>
<td>1.1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4[^e]</td>
<td>Et₂O</td>
<td>TMSOTf</td>
<td>2</td>
<td>50</td>
<td>85</td>
</tr>
<tr>
<td>5[^d]</td>
<td>DCM</td>
<td>TMSOTf</td>
<td>1.5</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>6[^d]</td>
<td>DCM</td>
<td>TMSOTf</td>
<td>2</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>7[^d]</td>
<td>DCM</td>
<td>TMSOTf</td>
<td>3</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>8[^e]</td>
<td>DCM</td>
<td>TMSOTf</td>
<td>1.5</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>9[^e]</td>
<td>DCM</td>
<td>TMSOTf</td>
<td>2</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>10[^e]</td>
<td>DCM</td>
<td>TMSOTf</td>
<td>3</td>
<td>100</td>
<td>93</td>
</tr>
</tbody>
</table>

[^a] The absolute configurations of products were determined on the basis of single-crystal X-ray diffraction analysis of compound 13a’ (see experimental section);[^b] NMR spectroscopy;[^c] Determined by chiral HPLC;[^d] 5 mol% of Cu/L1;[^e] 10 mol% Cu/L1.

Upon addition of TMSOTf to an ethereal solution of Cu/ligand complex and substrate 12a at -78 °C, formation of a precipitate was observed. Poor solubility of cationic intermediate 12a’ (Scheme 2) in the reaction media could be responsible for the moderate conversion reached in Et₂O. In support of this hypothesis, when DCM was used as solvent, no precipitate formation was detected and the substrate conversion increased drastically (Table 1, entry 5).

**Scheme 2: Formation of cationic species 12a’**.

Increasing the catalyst loading to 10 mol% resulted in higher conversion and better enantioselectivity, while higher excess of Grignard reagent improved only slightly the conversion (Table 1, entries 5-10). Having established the optimal LA for the activation of 12a, the effect of different solvents was investigated. All solvents tested, namely DCM, Et₂O, MTBE and toluene, were well tolerated providing the corresponding addition product 13a with excellent stereocontrol while conversion was strongly dependent on the nature of the solvent.
The best results were obtained when DCM was used as a solvent, with the product isolated in high yield (94%) and excellent ee (93%) (Table 2).

Table 2: Solvent screening.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conv. (%)</th>
<th>Yield (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂O</td>
<td>62</td>
<td>51</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>100</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>MTBE</td>
<td>67</td>
<td>55</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>79</td>
<td>64</td>
<td>87</td>
</tr>
</tbody>
</table>

[a] Reported yields are for isolated products; [b] Determined by chiral HPLC; Reaction conditions: 0.1 mmol of 12a, CuBr·SMe₂ (10 mol%), L1 (12 mol%), TMSOTf (3 equiv), EtMgBr (3 equiv), solvent (1 ml), -78 °C.

Finally, the optimization of the chiral ligand was assessed. Several diphosphine ligands belonging to the Josiphos family, with some example of BINAP derivatives, were tested under optimised reaction conditions (Table 3).

Table 3: Chiral ligand optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>Conv. (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;[c]&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;[d]&lt;/sup&gt;</th>
<th>Conv. (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;[c]&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;[d]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>77</td>
<td>N.D</td>
<td>-</td>
<td>7</td>
<td>L6</td>
<td>48</td>
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<tr>
<td>2</td>
<td>L1</td>
<td>100</td>
<td>94</td>
<td>93</td>
<td>8</td>
<td>L7</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>L2</td>
<td>76</td>
<td>61</td>
<td>45</td>
<td>9</td>
<td>L8</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>L3</td>
<td>75</td>
<td>38</td>
<td>0</td>
<td>10</td>
<td>L9</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>L4</td>
<td>ND</td>
<td>20</td>
<td>87</td>
<td>11</td>
<td>L10</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>L5</td>
<td>67</td>
<td>46</td>
<td>0</td>
<td>12</td>
<td>L11</td>
<td>80</td>
</tr>
</tbody>
</table>

[a] The absolute configurations of products were determined on the basis of single-crystal X-ray diffraction analysis of compound 13a' (see experimental section); [b] Determined by NMR spectroscopy; [c] Reported yields are for isolated products; [d] Determined by chiral HPLC.

All the tested ligands were able to promote the reaction to different extent. Ligands L3, L5 and L6 delivered the addition product 13a as a racemate. BINAP family ligands L10 and L11 afforded the addition product with good conversions but almost in racemic forms (Table 3, [91].
entries 11, 12). Having an electron rich diphenylphosphino moiety on the ethyl side chain seems to be beneficial for the enantioselectivity of the process (Table 3, entries 3, 8 vs 2, 9, 10). Finally ligand L4 led to a complex mixture from where was possible to obtain product 13a with 87% ee but only in 20% yield (Table 3, entry 5). Ligands L1, L8 and L9 performed better than the other catalysts tested, with ligand L1 being chosen as optimal ligand because of its slightly better performance (Table 3, entry 2 vs entries 9 and 10). With the optimal reaction conditions in our hands, the substrate scope was studied next. Different 4-alkenyl pyridines and 2-alkenyl pyridines were subjected to our protocol (Scheme 3). 4-Alkenyl pyridines 12a-d readily underwent conjugate addition, irrespective of the β-substituent on the double bond. Alkyl and aryl substituents, both electron rich and electron poor, at the β-position are well tolerated affording the corresponding alkylated products 13a-d in excellent yields and enantiopurities (Scheme 3). As expected 3-octenyl pyridine showed a complete lack of reactivity towards conjugated addition due to the missing resonance activation of the conjugated double bond (Scheme 3, 15a). Surprisingly, the same lack of reactivity was observed for 2-styryl pyridine and 2-octenyl pyridine (Scheme 3, 15b, 15c). Also in this case, no trace of product was detected in the crude NMR of the reaction mixture. Interestingly, introducing an ‘OTBDS’ group at the δ-position enhanced the reactivity sufficiently, thus providing the corresponding product 15d with high yield and ee (Scheme 3). Alkenyl pyridines bearing an electron withdrawing group on the aromatic ring required milder activation. In this case, use of BF₃⋅OEt₂ instead of TMSOTf reduced the amount of side products formation, providing the desired products with good yields and enantioselectivities (Scheme 3, 15e-i). The excellent chemoselectivity exhibited by our system allowed us to perform addition reactions in the presence of reactive functional groups known to be incompatible with hard organometallic reagents like Grignards. Substrates 14f and 14g, bearing respectively reactive functionalities such as ester and nitrile, delivered the corresponding addition products in good yields and high enantioselectivities with no significant amount of side products derived from the addition to the substituents (Scheme 3, 15f and 15g).
Scheme 3: Substrate scope. [a] Reported yields are for isolated products; [b] Determined by chiral HPLC; [c] The absolute configurations of products were determined on the basis of single-crystal X-ray diffraction analysis of compound 13a’ (see experimental section); [d] EtMgBr diluted in toluene and added dropwise over 2 hours; [e] BF$_3$·Et$_2$O is used as a LA; [f] ee of corresponding alcohol 13c’ after deprotection; [g] 5 mol% of catalyst used; [h] ee of the corresponding ether 21; [i] Small amount of unreacted substrate (≤ 9%) is not separable from product by chromatography. Yields are calculated by purity of product in the mixed fraction by NMR.

As already mentioned in the introduction of this chapter, the range of nucleophiles that can be employed with the known methodologies is narrow and the introduction of an aliphatic chain is not possible. To fill this blank space in the list of suitable nucleophiles for this transformation, we tested several aliphatic Grignard reagents with our catalytic system.
Table 5: Grignard reagent scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'MgX</th>
<th>R</th>
<th>Product</th>
<th>Yield (%) [b]</th>
<th>ee (%) [c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtMgBr</td>
<td>Ph</td>
<td>12a</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>PrMgCl</td>
<td>Ph</td>
<td>16a</td>
<td>75</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>HexMgBr</td>
<td>Ph</td>
<td>16b</td>
<td>81</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>i-PentMgBr</td>
<td>Ph</td>
<td>16c</td>
<td>65</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>i-BuMgBr</td>
<td>Hexyl</td>
<td>16d</td>
<td>56</td>
<td>64</td>
</tr>
<tr>
<td>6[d]</td>
<td>c-PentMgBr</td>
<td>Hexyl</td>
<td>16e</td>
<td>54</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>CH₂=CH(CH₃)₂MgBr</td>
<td>Hexyl</td>
<td>16f</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>CH₂=CH(CH₃)₂MgBr</td>
<td>Ph</td>
<td>16g</td>
<td>66</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>Ph(CH₂)₃MgBr</td>
<td>Hexyl</td>
<td>16h</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>10[e]</td>
<td>MeMgBr</td>
<td>Hexyl</td>
<td>16i</td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td>11[f]</td>
<td>PhMgBr</td>
<td>Hexyl</td>
<td>16j</td>
<td>84</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] The absolute configurations of products were determined on the basis of single-crystal X-ray diffraction analysis of compound 13a' (see experimental section); [b] Reported yields are for isolated products; [c] Determined by chiral HPLC; [d] 4 equiv of Grignard used; [e] Reaction was carried out at 0 °C for 5 h; [f] Ligand L10 was used.

For this purpose, substrates 12a and 12d were chosen as model compounds. Addition of all linear Grignard reagents afforded products 13a, 16a and 16b with good to excellent yields and ee’s showing no influence of the chain length on the reaction outcome (Table 5, entries 1-3). Bulkier α-, β-, and γ-branched Grignard reagents were also tolerated, providing the corresponding addition products with moderate to good yields and moderate to excellent enantioselectivities (Table 5, entries 4-6). From these results, no clear influence of steric hindrance can be deduced. Addition of γ- and α-branched Grignard reagents delivered the desired products respectively with 97% and 89% ee (Table 5, entries 4 and 6). An in-between ee value could be expected from the addition of the β-branched Grignard reagents. Counterintuitively, the enantioselectivity of this transformation dropped to 64% (Table 5, entry 5). Grignard reagents bearing olefinic or aromatic moieties proved to be suitable nucleophiles affording the corresponding products 16f, 16g and 16h with good to excellent ee’s (Table 5, entries 7-9). Introduction of methyl substituent via addition of MeMgBr, is often a troublesome transformation due to the low reactivity of the organometallic reagent. Nevertheless, thanks to the strong activation provided by the TMSOTf, MeMgBr was added successfully when compound 12d was subjected to our protocol at 0 °C. Addition product 16i was obtained with high enantioselectivity but in moderate yield, due to troublesome chromatographic separation between the product and unreacted substrate (Table 5, entry 10). Finally, also aromatic Grignard reagents were tested. Addition of PhMgBr proceeded smoothly delivering product 16j in good yield but unfortunately as racemate (Table 5, entry 11).

Next, to evaluate the robustness of our methodology, a series of experiments were carried out for the addition of EtMgBr to 12a.
Performing the reaction on a 30-fold larger scale did not affect the outcome of the reaction and the product 13a was isolated with the same excellent yield (94%) and ee (94%) as for the 0.1 mmol scale reaction (Scheme 4). Remarkably, the catalyst recovered from this reaction, as a copper complex, can be recycled delivering product 13a with only minor deviation from the original results. To conclude these studies, the influence of temperature was investigated next (Table 6).

Table 6: Influence of the temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>96</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>91</td>
<td>79</td>
</tr>
</tbody>
</table>

Reaction conditions: 12a (0.1mmol), CuBr·SMe₂ (10 mol%), L1 (12 mol%), TMSOTf (3 equiv), EtMgBr (3 equiv), DCM (1ml).

Interestingly, this catalytic system showed a better tolerance for higher temperature compared with the one discussed in Chapter 2. As already mentioned, when BF₃·OEt₂ is used as an additive in presence of Grignard reagents, temperatures below -50 °C are required in order to avoid the reaction between themselves, which outcompetes the desired conjugate addition. TMSOTf reacts with Grignard reagents at lower rate than BF₃·OEt₂, thus allowing to carry out the transformation at room temperature without the reaction between TMSOTf and EtMgBr taking over on the addition process. In this case, product 13a was obtained in excellent yield but with a significant decrease in enantioselectivity (Table 6, entry 3). Reducing the temperature to 0 °C improved slightly the ee to 83% (Table 6, entry 2).

As already shown, the high functional group tolerance exhibited by this catalytic system allowed us to perform alkylation of pyridines bearing reactive functional groups. This gave us the possibility to functionalise further the corresponding alkylated products (Scheme 5). Piperidine derivative 17 can be obtained in quantitative yield from compound 13a by selective reduction of the pyridine by simple hydrogenation (Scheme 5a). Subjecting compound 15i to [3+2] cycloaddition in presence of NaN₃ delivered tetrazole derivative 18 in good yield (Scheme 5b).

Product 15i, which has a bromo substituent on the pyridine ring, can be employed in several transformations. Upon treatment of 15i with ethyl acrylate in presence of Pd catalyst, the corresponding Heck coupling product 19 was obtained (Scheme 5c). Treating 15i with BF₃·OEt₂ and iPrMgCl-LiCl complex led to direct alkylation of the pyridine ring (Scheme 5d). Another direct functionalisation of the pyridine ring, leading to the formation of pyridyl-ether 21 through pyridyl-phosphonium salt, could be achieved using a very recent two step methodology developed by McNally and co-workers (Scheme 5e).
4.3 Conclusion

We have demonstrated that less reactive alkenyl-pyridines can be used as Michael acceptors for enantioselective nucleophilic addition of Grignard reagents. The process exhibits a high functional group tolerance, a broad substrate scope including 4-alkenyl and 2-alkenyl pyridines with various substituents both on the aromatic ring and the β-position, as well as a broad Grignard-scope including linear, branched, and functionalised examples. Importantly, enantioselective methylation of conjugated alkenyl-pyridines is possible by using the least reactive Grignard reagent (MeMgBr), which is generally considered very difficult. Finally, these reactions can be carried out in the most common solvents and on comparatively large scales, while cryogenic conditions can be avoided. Several of the obtained chiral pyridine products could be transformed straightforwardly into diverse products, due to the remarkable functional group tolerance exhibited by this catalytic system.
4.4 Experimental Section

4.4.1 General Information

All reactions using oxygen- and/or moisture-sensitive materials were carried out with anhydrous solvents (vide infra) under a nitrogen atmosphere using oven dried glassware and standard Schlenk techniques. Reactions were monitored by $^1$H NMR. Purification of the products, when necessary, was performed by flash-column chromatography using Merck 60 Å 230-400 mesh silica gel. NMR data was collected on Varian VXR400 ($^1$H at 400.0 MHz; $^{13}$C at 100.58 MHz, $^{19}$F at 376.29, $^{31}$P at 161.94 MHz), equipped with a 5 mm $z$-gradient broadband probe. Chemical shifts are reported in parts per million (ppm) relative to residual solvent peak (CDCl$_3$, $^1$H: 7.26 ppm; $^{13}$C: 77.16 ppm). Coupling constants are reported in Hertz. Multiplicity is reported with the usual abbreviations (s: singlet, bs: broad singlet, d: doublet, dd: doublet of doublets, ddd: doublet of doublet of doublets, t: triplet, td: triplet of doublets, q: quartet, dq: doublet of quartet, p: pentet, sex: sextet, hept: heptet, m: multiplet). Exact mass spectra were recorded on a LTQ Orbitrap XL apparatus with ESI ionization. Enantiomeric excesses (ee’s) were determined by Chiral HPLC analysis using a Shimadzu LC-10AD VP HPLC equipped with a Shimadzu SPD-M10A VP diode array detector and by Waters Acquity UPC2 system with PDA detector and QDA mass detector. For the X-ray measurement a Bruker-AXS D8 Venture diffractometer was used. The structures were solved by direct methods using SHELXT10 and refinement of the structure was performed using SHELXL.11 Unless otherwise indicated, reagents and substrates were purchased from commercial sources and used as received. Solvents not required to be dry were purchased as technical grade and used as received. Dry solvents were freshly collected from a dry solvent purification system prior to use. Inert atmosphere experiments were performed with standard Schlenk techniques with dried (P$_2$O$_5$) nitrogen gas. Grignard reagents were purchased from Sigma-Aldrich and used as received (EtMgBr (3M in Et$_2$O), ButMgBr, nPropylMgCl, HexMgBr, iPentMgBr, iButMgBr, cyclopentylMgBr (2M in Et$_2$O). All other Grignard reagents were prepared from the corresponding alkyl bromides and Mg activated with I$_2$ in Et$_2$O and concentration was determined by NMR titration method.12 (but-3-en-1-ylMgBr (2M in Et$_2$O), pent-4-en-1-ylMgBr (1.8M in Et$_2$O), phenethylMgBr (2.6 M in Et$_2$O). Unless otherwise noted substrates were prepared by literature reported methods (vide infra). Chiral ligands (L1 - L6 and L10 - L11) were purchased from Sigma Aldrich and Solvias. All reported compounds were characterized by $^1$H and $^{13}$C NMR and compared with literature data. All new compounds were fully characterized by $^1$H and $^{13}$C NMR and HRMS techniques. The absolute configurations of products were determined on the basis of single-crystal X-ray diffraction analysis of compound 13a’ derived from 13a and the stereochemistry was assigned to be ‘S’.

4.4.2 Synthesis and Characterizations of Substrates

(E)-4-styrylpyridine (12a)

![Image](image-url)

Compound 12a was synthesized according to the literature procedure.13 The product was obtained as a white solid after flash-column chromatography (pentane:EtOAc, 80:20, v/v). Yield = 63%. The NMR data are in agreement with the one present in literature.14
$^{1}$H NMR (400 MHz, CDCl$_3$) δ 8.58 (d, $J$ = 5.1 Hz, 2H), 7.55 (d, $J$ = 7.0 Hz, 2H), 7.44 – 7.34 (m, 5H), 7.31 (d, $J$ = 16.0 Hz, 1H), 7.02 (d, $J$ = 16.3 Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 152.8, 147.3, 138.8, 135.8, 131.5, 131.4, 129.7, 128.6, 123.5.

HRMS (ESI$^+$): $m/z$ calcd. for C$_{13}$H$_{12}$N ([M+H$^+$]) 182.09643, found 182.09655.

(E)-4-(4-(trifluoromethyl)styryl)pyridine (12b)

Compound 12b was synthesized according to the literature procedure.$^{13}$ The product was obtained as a white solid after flash-column chromatography (pentane:EtOAc, 60:40, v/v). Yield = 11%. The NMR data are in agreement with the one present in literature.$^{15}$

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 8.62 (d, $J$ = 5.2 Hz, 2H), 7.64 (s, 4H), 7.39 (d, $J$ = 5.0 Hz, 2H), 7.32 (d, $J$ = 16.3 Hz, 1H), 7.10 (d, $J$ = 16.4 Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 150.3, 143.9, 139.6 (q, $J$ = 1.3 Hz), 131.5, 130.3 (q, $J$ = 32.5 Hz), 128.5, 127.1, 125.8 (q, $J$ = 3.9 Hz), 124.1 (q, $J$ = 272.0 Hz), 121.0.

$^{19}$F NMR (376 MHz, CDCl$_3$) δ -62.61.

(E)-4-(4-(tert-butyldimethylsilyl)but-1-en-1-yl)pyridine (12c)

Compound 12c was synthesized according to the literature procedure.$^{13}$ The product was isolated as colorless oil after flash-column chromatography (pentane:EtOAc, 80:20 → 60:40, v/v). Yield = 86%.

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 8.45 (d, $J$ = 6.2 Hz, 2H), 7.14 (d, $J$ = 6.2 Hz, 2H), 6.44 (dt, $J$ = 16.1, 6.8 Hz, 1H), 6.32 (d, $J$ = 16.0 Hz, 1H), 3.70 (t, $J$ = 6.5 Hz, 2H), 2.44 (q, $J$ = 6.6 Hz, 2H), 0.85 (s, 9H), 0.02 (s, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 150.0, 144.9, 134.9, 139.6 (q, $J$ = 1.3 Hz), 131.5, 130.3 (q, $J$ = 32.5 Hz), 128.5, 127.1, 125.8 (q, $J$ = 3.9 Hz), 124.1 (q, $J$ = 272.0 Hz), 121.0.

HRMS (ESI$^+$): $m/z$ calcd. for C$_{15}$H$_{26}$NOSi ([M+H$^+$]) 264.17782, found 264.17769.

(E)-4-(oct-1-en-1-yl)pyridine (12d)

Compound 12d was synthesized according to the literature procedure.$^{13}$ The product was isolated as colorless oil after flash-column chromatography (pentane:EtOAc, 80:20 → 60:40, v/v). Yield = 86%.

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 8.43 (d, $J$ = 6.1 Hz, 2H), 7.12 (d, $J$ = 6.1 Hz, 2H), 6.40 (dt, $J$ = 15.5, 6.9 Hz, 1H), 6.23 (d, $J$ = 15.9 Hz, 1H), 2.16 (q, $J$ = 7.3 Hz, 2H), 1.41 (p, $J$ = 7.2 Hz, 2H), 1.34 – 1.16 (m, 6H), 0.84 (t, $J$ = 6.7 Hz, 3H).
(E)-2-((4-(tert-butyldimethylsilyl)but-1-en-1-yl)pyridine (14d)

Compound 14d was synthesized according to the literature procedure. The product was isolated as colorless oil after flash-column chromatography (pentane:EtOAc, 97:3 → 93:7, v/v), Yield = 90%

H NMR (400 MHz, CDCl₃) δ 8.51 (d, J = 4.9 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 6.7 Hz, 1H), 7.14 – 7.02 (m, 1H), 6.70 (dt, J = 15.8, 7.0 Hz, 1H), 6.53 (d, J = 15.8 Hz, 1H), 3.75 (t, J = 6.9 Hz, 2H), 2.48 (q, J = 6.9 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

C NMR (101 MHz, CDCl₃) δ 156.0, 149.5, 136.5, 132.0, 131.9, 121.8, 121.0, 62.8, 36.6, 26.1, 18.5, -5.1.

HRMS (ESI+): m/z calcd. for C₁₃H₂₀N ([M+H⁺]) 190.15903, measured mass: 190.15890.

(E)-2-((oct-1-en-1-yl)-5-(trifluoromethyl)pyridine (14e)

Compound 14e was synthesized according to the literature procedure. The product was isolated as colorless oil after flash-column chromatography (pentane:EtOAc, 99:1, v/v), Yield = 56%

H NMR (400 MHz, CDCl₃) δ 8.76 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 8.3, 2.3 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 6.89 (dt, J = 15.6, 7.0 Hz, 1H), 6.52 (d, J = 15.6 Hz, 1H), 2.29 (q, J = 7.1 Hz, 2H), 1.51 (p, J = 7.2 Hz, 2H), 1.42 – 1.21 (m, 6H), 0.88 (t, J = 6.7 Hz, 3H).

C NMR (101 MHz, CDCl₃) δ 159.5, 146.4 (q, J = 4.2 Hz), 139.6, 133.9, 133.7, 133.5 (q, J = 3.5 Hz), 128.9, 128.8, 128.6, 128.5, 124.1 (q, J = 32.9 Hz), 123.9 (q, J = 271.75 Hz), 120.4, 33.0, 31.8, 29.1, 28.9, 22.7, 14.1.

F NMR (376 MHz, CDCl₃) δ -62.3.

HRMS (ESI+): m/z calcd. for C₁₄H₁₈F₃N ([M+H⁺]) 258.14641, measured mass: 258.14651

Ethyl (E)-6-((oct-1-en-1-yl)nicotinate (14f)

Compound 14f was synthesized according to the literature procedure. As the product was isolated as the corresponding carboxylic acid it was subjected to the esterification protocol: the acid was dissolved in MeOH and thionylchloride was added dropwise at 0 °C, reaction was warmed to room temperature and kept stirring for additional 2 h. The reaction mixture was poured in H₂O and extracted with EtOAc. The organic layer was then washed with NaHCO₃ and
dried on MgSO$_4$, volatiles were removed on rotary evaporator. The compound 14f was obtained as colorless oil after flash-column chromatography (pentane:EtOAc, 90:10, v/v), Yield = 56%

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.07 (d, $J = 2.2$ Hz, 1H), 8.13 (dd, $J = 8.2$, 2.2 Hz, 1H), 7.23 (d, $J = 8.2$ Hz, 1H), 6.86 (dt, $J = 15.6$, 7.0 Hz, 1H), 6.48 (d, $J = 15.7$ Hz, 1H), 3.88 (s, 3H), 2.24 (q, $J = 7.0$ Hz, 2H), 1.46 (p, $J = 6.9$ Hz, 2H), 1.38 – 1.15 (m, 6H), 0.84 (t, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 165.9, 159.8, 150.8, 139.5, 137.5, 129.3, 123.5, 120.4, 52.2, 33.1, 31.7, 29.0, 28.8, 22.6, 14.1.

HRMS (ESI$^+$): $m/z$ calcd. for C$_{15}$H$_{22}$NO$_2$ ([M+H$^+$]) 248.16451, found 248.16433

(E)-6-(oct-1-en-1-yl)nicotinonitrile (14g)

Compound 14g was synthesized according to the literature procedure.$^{13}$ The product was isolated as colorless oil after flash-column chromatography (pentane:DCM, 60:40 $\rightarrow$ 50:50, v/v), Yield = 84%

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.68 (d, $J = 2.1$ Hz, 1H), 7.77 (dd, $J = 8.2$, 2.2 Hz, 1H), 7.23 (d, $J = 8.2$ Hz, 1H), 6.90 (dt, $J = 15.7$, 7.1 Hz, 1H), 6.43 (d, $J = 15.6$ Hz, 1H), 2.22 (q, $J = 7.2$ Hz, 2H), 1.43 (p, $J = 6.9$ Hz, 2H), 1.36 – 1.11 (m, 6H), 0.81 (t, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 159.2, 152.1, 141.1, 139.4, 128.6, 120.5, 117.1, 106.8, 32.9, 31.6, 28.9, 28.6, 22.5, 14.0.

HRMS (ESI$^+$): $m/z$ calcd. for C$_{14}$H$_{19}$N$_2$ ([M+H$^+$]) 215.15428, found 215.15454

(E)-5-chloro-2-(oct-1-en-1-yl)pyridine (14h)

Compound 14h was synthesized according to the literature procedure.$^{13}$ The product was isolated as colorless oil after flash-column chromatography (pentane:EtOAc, 99:1 v/v), Yield = 79%

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.44 (s, 1H), 7.53 (dt, $J = 8.4$, 2.9 Hz, 1H), 7.15 (dd, $J = 8.5$, 2.8 Hz, 1H), 6.70 (dt, $J = 14.1$, 7.0 Hz, 1H), 6.41 (d, $J = 13.9$ Hz, 1H), 2.23 (q, $J = 7.2$ Hz, 2H), 1.47 (p, 2H), 1.40 – 1.16 (m, 6H), 0.87 (t, $J = 6.2$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 154.5, 148.2, 137.0, 136.1, 129.5, 128.8, 121.5, 32.9, 31.8, 29.0, 28.9, 22.7, 14.2.

HRMS (ESI$^+$): $m/z$ calcd. for C$_{13}$H$_{15}$ClN ([M+H$^+$]) 224.12005, found 224.12066
(E)-5-bromo-2-(oct-1-en-1-yl)pyridine (14i)

Compound 14i was synthesized according to the literature procedure. The product was isolated as colorless oil after flash-column chromatography (pentane:EtOAc, 99:1, v/v), Yield = 67%

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.55 (d, $J = 2.3$ Hz, 1H), 7.68 (dd, $J = 8.4, 2.3$ Hz, 1H), 7.11 (d, $J = 8.4$ Hz, 1H), 6.72 (dt, $J = 16.0, 6.9$ Hz, 1H), 6.40 (d, $J = 15.7$ Hz, 1H), 2.23 (q, $J = 7.3$ Hz, 2H), 1.48 (m, 2H), 1.39 – 1.16 (m, 6H), 0.87 (t, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.8, 150.4, 138.9, 137.2, 128.8, 122.1, 118.1, 33.0, 31.8, 29.1, 29.0, 22.7, 14.2.

HRMS (ESI$^+$): $m/z$ calcld. for C$_{13}$H$_{19}$BrN ([M+H$^+$]) 268.06954, found 268.06967

4.4.3 General Procedure A: Cu-Catalyzed Asymmetric Grignard Addition to 4-Alkenyl Pyridines.

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr·SMe$_2$ (0.10 equiv), and ligand ($R$,S$_p$)-L1 (0.12 equiv) were dissolved in DCM (1mL/0.1mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (1.0 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C and TMSOTf or BF$_3$·OEt$_2$ (2.0 – 3.0 equiv) was added followed by RMgX (3.0 equiv). After stirring at -78 °C for 16h, the reaction was quenched as above and purified by flash chromatography on silica using mixture of pentane and EtOAc as eluent.

4.4.4 General Procedure B: Cu-Catalyzed Asymmetric Grignard Addition to 2-Alkenyl Pyridines.

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr·SMe$_2$ (0.10 equiv), and ligand ($R$,S$_p$)-L1 (0.12 equiv) were dissolved in Et$_2$O or DCM (1mL/0.1mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (1.0 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C and BF$_3$·OEt$_2$ (1.5 equiv) was added followed by RMgX (2.0 equiv). After stirring at -78 °C for 16h, the reaction was quenched as above and purified by flash chromatography on silica using mixture of pentane and EtOAc as eluent.
4.4.5 General Procedure C: Synthesis of Racemic Products

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr·SMe₂ (0.10 equiv), and (±) BINAP (0.12 equiv) were dissolved in DCM (1mL/0.1mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (1.0 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C and TMSOTf (3.0 equiv) or BF₃·OEt₂ (1.5 equiv) was added followed by RMgX (1.5 – 3.0 equiv). After stirring at -78 °C for 16h, the reaction was quenched as above and purified by flash chromatography on silica using mixture of pentane and EtOAc as eluent.

Notes:
a) Unless otherwise noted all products were isolated as pale-yellow oil; b) For liquid/oily substrates, CuBr·SMe₂ and ligand (R,Sₚ)-L₁ were dissolved in 0.7 ml of Et₂O/DCM while the remaining 0.3 ml of Et₂O/DCM was employed to transfer the substrate in the reaction Schlenk tube.

4.4.6 Synthesis and Characterizations of Products (13a-d, 15a-f, and 16a-j)

(S)-4-(2-phenylbutyl)pyridine (13a)

The reaction was performed using general procedure A, with 0.1 mmol 12a, TMSOTf (0.3 mmol, 3.0 equiv), EtMgBr (3M in Et₂O, 0.3 mmol, 3.0 equiv), CuBr·SMe₂ (0.01 mmol, 10 mol%), ligand (R,Sₚ)-L₁ (0.012 mmol, 12 mol%) in 1mL DCM. Product 13a was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc 80:20, v/v), [94% yield, 93% ee].

1H NMR (400 MHz, CDCl₃) δ 8.39 (d, J = 5.0 Hz, 2H), 7.29 – 7.21 (m, 2H), 7.21 – 7.12 (m, 1H), 7.06 (d, J = 6.8 Hz, 2H), 6.91 (d, J = 6.1 Hz, 2H), 2.97 – 2.78 (m, 2H), 2.78 – 2.65 (m, 1H), 1.79 – 1.58 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H).

13C NMR (101 MHz, CDCl₃) δ 149.8, 149.6, 143.9, 128.5, 127.9, 126.5, 124.7, 49.2, 42.8, 28.9, 12.1.

HRMS (ESI⁺): m/z calcd. for C₁₅H₁₅N ([M+H⁺]) 212.14338, found 212.14315

CSP-HPLC: (254 nm, Chiralcel OZ-H, n-heptane:iPrOH = 95:5, 40 °C, 1.0 ml/min.), tₘ = 9.61 min (major), tₙ = 10.27 min (minor).

(S)-4-(2-(4-(trifluoromethyl)phenyl)butyl)pyridine (13b)

The reaction was performed using general procedure A, with 0.1 mmol 12b, TMSOTf (0.3 mmol, 3.0 equiv), CuBr·SMe₂ (0.01 mmol, 10 mol%), ligand (R,Sₚ)-L₁ (0.012 mmol, 12 mol%) in 1mL DCM. EtMgBr (3M in Et₂O, 0.3 mmol, 3.0 equiv) diluted to 0.35 mL toluene and added by syringe.
pump for 2h. Product 13b was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc 80:20, v/v), [87% yield, 89% ee].

\[ ^1H\text{ NMR} (400\text{ MHz, CDCl}_3) \delta 8.41 (s, 2H), 7.50 (d, J = 8.0 \text{ Hz, 2H}), 7.17 (d, J = 8.1 \text{ Hz, 2H}), 6.90 (d, J = 5.0 \text{ Hz, 2H}), 3.05-2.89 (m, 1H), 2.87–2.77 (m, 2H), 1.83–1.60 (m, 2H), 0.79 (t, J = 7.4 \text{ Hz, 3H}). \]

\[ ^{13}C\text{ NMR} (101\text{ MHz, CDCl}_3) \delta 149.74, 149.68, 149.10, 148.10, 128.20, 125.70 (q, J = 5.7 \text{ Hz}), 125.40, 49.10, 42.50, 28.80, 12.10. \]

\[ ^{19}F\text{ NMR} (376\text{ MHz, CDCl}_3) \delta -62.40. \]

HRMS (ESI⁺): \(m/z\) calcd. for C₁₆H₁₇F₃N ([M+H⁺]) 280.13076, found 280.13146.

CSP-HPLC: (206 nm, Chiralcel OZ-H, n-heptane:iPrOH = 95:5, 40 °C, 0.5 ml/min.), \(t_R = 21.72\text{ min (major)}, t_R = 22.58\text{ min (minor)}. \]

\((S)-4-(4-(tert-butyldimethylsilyl)-2-ethylbutyl)pyridine (13c)\)

\[
\text{N} \quad \text{CH}_2 \quad \text{Si(OCH)}_3
\]

The reaction was performed using general procedure A, with 0.1 mmol 12c, BF₃·OEt₂ (0.2 mmol, 2.0 equiv), EtMgBr (3M in Et₂O, 0.3 mmol, 3.0 equiv), CuBr·SMe₂ (0.01 mmol, 10 mol%), ligand \((R,S_p)-L1\) (0.012 mmol, 12 mol%) in 1mL DCM. Product 13c was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc 90:10 → 85:15, v/v), [82% yield, 97% ee, ee measured after deprotection, see compound 13c’]

\[ ^1H\text{ NMR} (400\text{ MHz, CDCl}_3) \delta 8.49 (s, 2H), 7.09 (d, J = 4.7 \text{ Hz, 2H}), 3.79 – 3.49 (m, 2H), 2.55 (d, J = 7.2 \text{ Hz, 2H}), 1.88 – 1.67 (m, 1H), 1.62 – 1.36 (m, 2H), 1.37 – 1.20 (m, 2H), 0.90 (t, J =6.9 \text{ Hz, 3H}), 0.88 (s, 9H), 0.02 (d, J = 3.0 \text{ Hz, 6H}). \]

\[ ^{13}C\text{ NMR} (101\text{ MHz, CDCl}_3) \delta 150.80, 149.60, 124.90, 61.20, 39.70, 37.30, 36.00, 26.10, 25.80, 18.40, 10.80. \]

HRMS (ESI⁺): \(m/z\) calcd. for C₁₇H₃₂NOSi ([M+H⁺]) 294.22477, found 294.22483.

\((S)-3-(pyridin-4-ylmethyl)pentan-1-ol (13c')\)

\[
\text{N} \quad \text{CH}_2 \quad \text{OH}
\]

In flame dried Schelnk, 0.17 mmol of 13c were dissolved in THF (0.3 ml). The reaction mixture was cooled to 0 °C and a TBAF solution (1M in THF) was added dropwise. The reaction mixture stirred for 4 h while warming to RT. The crude was quenched with H₂O and extracted with EtOAc. The organic layer was dried on MgSO₄. Product 13c’ was obtained as a pale-yellow oil after flash-column chromatography (SiO₂ EtOAc → MeOH) [36% yield, 97% ee].

\[ ^1H\text{ NMR} (400\text{ MHz, CDCl}_3) \delta 8.44 (d, J = 4.9 \text{ Hz, 2H}), 7.09 (d, J = 5.0 \text{ Hz, 2H}), 3.74 – 3.57 (m, 2H), 2.69 – 2.46 (m, 2H), 1.96 (s, 1H), 1.86 – 1.71 (m, 1H), 1.65 – 1.43 (m, 2H), 1.41 – 1.18 (m, 2H), 0.90 (t, J = 7.4 \text{ Hz, 3H}). \]

\[ ^{13}C\text{ NMR} (101\text{ MHz, CDCl}_3) \delta 150.60, 149.60, 124.80, 60.80, 39.70, 37.30, 36.00, 25.80, 10.80. \]
HRMS (ESI⁺): m/z calcd. for C₁₁H₁₈NΟ ([M+H⁺]) 180.13829, found 180.13824.

CSP-HPLC: (254 nm, Chiralcel AY-H, n-heptane:iPrOH = 95:5, 40 °C, 0.5 ml/min.), t_R = 22.89 min (minor), t_R = 23.99 min (major).

(R)-4-(2-ethyloctyl)pyridine (13d)

The reaction was performed using general procedure A, with 0.1 mmol 12d, TMSOTf (0.3 mmol, 3.0 equiv), EtMgBr (3M in Et₂O, 0.3 mmol, 3.0 equiv), CuBr-SMe₂ (0.01 mmol, 10 mol%), ligand (R,S)p-L1 (0.012 mmol, 12 mol%) in 1mL DCM. Product 13d was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc 80:20, v/v), [86% yield, 93% ee].

¹H NMR (400 MHz, CDCl₃) δ 8.48 (s, 2H), 7.07 (d, J = 4.6 Hz, 2H), 2.51 (d, J = 7.1 Hz, 2H), 1.66 – 1.52 (m, 1H), 1.42 – 1.11 (m, 12H), 0.86 (t, J = 7.2 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 151.1, 149.6, 124.8, 40.6, 39.7, 32.8, 32.0, 29.7, 26.7, 25.6, 22.8, 14.2, 10.9.

HRMS (ESI⁺): m/z calcd. for C₁₅H₂₆N ([M+H⁺]) 220.20598, found 220.20575

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane:iPrOH = 99.2:0.8, 40 °C, 0.5 ml/min.), t_R = 25.37 min (major), t_R = 26.11 min (minor).

(S)-2-(4-(tert-butyldimethylsilyl)-2-ethylbutyl)pyridine (15d)

The reaction was performed using general procedure A, with 0.1 mmol 14d, TMSOTf (0.3 mmol, 3.0 equiv), CuBr-SMe₂ (0.01 mmol, 10 mol%), ligand (R,S)p-L1 (0.012 mmol, 12 mol%) in 1mL DCM. EtMgBr (3M in Et₂O, 0.4 mmol, 4.0 equiv) diluted to 0.45 mL in toluene and added over a period of 2h. Product 15d was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc 98:2, v/v), [74% yield, 89% ee].

¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, J = 4.9 Hz, 1H), 7.56 (td, J = 7.7, 1.9 Hz, 1H), 7.16 – 7.04 (m, 2H), 3.68 – 3.53 (m, 2H), 2.73 (qd, J = 13.5, 7.3 Hz, 2H), 1.98 – 1.88 (m, 1H), 1.61 – 1.42 (m, 2H), 1.40 -1.27 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H), 0.86 (s, 9H), 0.00 (d, J = 3.4 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 161.7, 149.3, 136.1, 123.7, 121.0, 61.6, 43.0, 37.1, 36.2, 26.2, 26.1, 18.4, 10.9, -5.1.

HRMS (ESI⁺): m/z calcd. for C₁₇H₃₃NOSi ([M+H⁺]) 294.22477, found 294.22502

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane:iPrOH = 99.2:0.8, 40 °C, 0.5 ml/min.), t_R = 9.96 min (minor), t_R = 10.55 min (major).
(R)-2-(2-ethyloctyl)-5-(trifluoromethyl)pyridine (15e)

The reaction was performed using general procedure B, with 0.38 mmol 14e, BF$_3$-OEt$_2$ (0.57 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.57 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.019 mmol, 5 mol%), ligand (R,S$_p$)-L1 (0.023 mmol, 6 mol%) in 4mL Et$_2$O. Product 15e was obtained as pale-yellow oil after flash-column chromatography (SiO$_2$, pentane:EtOAc 99:1, v/v), [60% yield, 99% ee, ee measured after further functionalization, see compound 21]

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.78 (d, $J = 2.3$ Hz, 1H), 7.79 (dd, $J = 8.2, 2.3$ Hz, 1H), 7.23 (d, $J = 8.1$ Hz, 1H), 2.77 (d, $J = 7.2$ Hz, 2H), 1.84 (hept, $J = 6.5$ Hz, 1H), 1.40 – 1.10 (m, 12H), 0.86 (q, $J = 7.3$ Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.4, 146.2 (q, $J = 4.1$ Hz), 133.1 (q, $J = 3.4$ Hz), 124.0 (q, $J = 32.9$ Hz), 124.0 (q, $J = 271.9$ Hz), 123.3, 42.9, 40.1, 32.9, 32.0, 29.7, 26.6, 25.8, 22.8, 14.2, 10.8.

$^{19}$F NMR (376 MHz, CDCl$_3$) δ -62.3.

HRMS (ESI$^+$): m/z calcd. for C$_{16}$H$_{25}$F$_3$N ([M+H$^+$]) 288.19336, found 288.19397

Methyl (R)-6-(2-ethyloctyl)nicotinate (15f)

The reaction was performed using general procedure B, with 0.1 mmol 14f, BF$_3$-OEt$_2$ (0.11 mmol, 1.1 equiv), EtMgBr (3M in Et$_2$O, 0.12 mmol, 1.2 equiv), CuBr·SMe$_2$ (0.01 mmol, 10 mol%), ligand (R,S$_p$)-L1 (0.012 mmol, 12 mol%) in 1mL Et$_2$O. Product 15f was obtained as pale-yellow oil after flash-column chromatography (SiO$_2$, pentane:EtOAc 90:10, v/v), [93% yield, 89% ee]

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.12 (d, $J = 2.2$ Hz, 1H), 8.16 (dd, $J = 8.1, 2.3$ Hz, 1H), 7.19 (d, $J = 8.1$ Hz, 1H), 3.92 (s, 3H), 2.76 (d, $J = 7.6$ Hz, 2H), 1.91 – 1.77 (m, 1H), 1.38 – 1.13 (m, 12H), 0.85 (td, $J = 7.2, 4.8$ Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.0, 166.2, 150.6, 137.1, 123.5, 123.3, 52.3, 43.1, 40.1, 33.0, 32.0, 29.8, 26.6, 25.9, 22.8, 14.2, 10.8.

HRMS (ESI$^+$): m/z calcd. for C$_{17}$H$_{28}$NO$_2$ ([M+H$^+$]) 278.21146, found 278.21169

CSP-HPLC: (238 nm, Chiralcel OZ-H, n-heptane/iPrOH = 99.2:0.8, 40 °C, 0.5 ml/min.), $t_R$ = 53.02 min (minor), $t_R$ = 59.09 min (major)
(R)-6-(2-ethylcycloctyl)nicotinonitrile (15g)

The reaction was performed using general procedure B, with 0.3 mmol 14g, BF₃·OEt₂ (0.45 mmol, 1.5 equiv), EtMgBr (3M in Et₂O, 0.6 mmol, 2.0 equiv), CuBr·SMe₂ (0.03 mmol, 10 mol%), ligand (R,S₆)-L₁ (0.036 mmol, 12 mol%) in 3mL DCM. Product 15g was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc 98:2, v/v), [64% yield, 87% ee]

¹H NMR (400 MHz, CDCl₃) δ 8.81 (s, 1H), 7.84 (dd, J = 8.1, 2.2 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 2.77 (d, J = 7.2 Hz, 2H), 1.84 (p, J = 6.4 Hz, 1H), 1.36 – 1.16 (m, 12H), 0.87 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 167.0, 152.2, 139.1, 123.7, 117.2, 107.1, 43.2, 40.1, 33.0, 32.0, 29.9, 26.6, 25.9, 22.8, 14.2, 10.8.

HRMS (ESI⁺): m/z calcd. for C₁₆H₂₅N₂ ([M+H⁺]) 245.20123, found 245.20186

CSP-HPLC: (224 nm, Chiralcel AY-H, n-heptane:iPrOH = 99.7:0.3, 40 °C, 0.25 ml/min.), tₘₐₗ₉ = 24.34 min (major), tₘᵢₙᵢᵢᵦ = 30.96 min (minor)

(R)-5-chloro-2-(2-ethylcycloctyl)pyridine (15h)

The reaction was performed using general procedure B, with 0.1 mmol 14h, BF₃·OEt₂ (0.15 mmol, 1.5 equiv), EtMgBr (3M in Et₂O, 0.2 mmol, 2.0 equiv), CuBr·SMe₂ (0.01 mmol, 10 mol%), ligand (R,S₆)-L₁ (0.012 mmol, 12 mol%) in 1mL DCM. Product 15h was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc 98:2, v/v), [59% yield, 95% ee]

¹H NMR (400 MHz, CDCl₃) δ 8.48 (d, J = 2.5 Hz, 1H), 7.54 (dd, J = 8.3, 2.5 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H), 2.67 (d, J = 7.3 Hz, 2H), 1.83 – 1.70 (m, 1H), 1.41 – 1.16 (m, 12H), 0.86 (t, J = 7.3 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 160.3, 148.1, 135.8, 129.2, 124.4, 42.1, 40.1, 32.9, 32.0, 29.8, 26.6, 25.7, 22.8, 14.3, 10.8.

HRMS (ESI⁺): m/z calcd. for C₁₅H₂₃ClN ([M+H⁺]) 254.16700, found 254.16497

CSP-HPLC: (217 nm, Chiralcel AD-H, n-heptane:iPrOH = 99.9:0.1, 40 °C, 0.25 ml/min.), tₘₐₗ₉ = 20.68 min (major), tₘᵢₙᵢᵦ = 21.56 min (minor)

(R)-5-bromo-2-(2-ethylcycloctyl)pyridine (15i)

The reaction was performed using general procedure B, with 0.1 mmol 14i, BF₃·OEt₂ (0.15 mmol, 1.5 equiv), EtMgBr (3M in Et₂O, 0.2 mmol, 2.0 equiv), CuBr·SMe₂ (0.01 mmol, 10 mol%),
ligand \((R,S_p)-L1\) (0.012 mmol, 12 mol\%) in 1mL DCM. Product 15i was obtained as pale-yellow oil after flash-column chromatography (SiO\(_2\), pentane:EtOAc 98:2, v/v), [75\% yield, 99\% ee].

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.58 (dd, \(J = 2.5, 0.7\) Hz, 1H), 7.68 (dd, \(J = 8.2, 2.5\) Hz, 1H), 7.01 (dd, \(J = 8.2, 0.7\) Hz, 1H), 2.65 (d, \(J = 7.2\) Hz, 2H), 1.77 (p, \(J = 7.1\) Hz, 1H), 1.37 – 1.17 (m, 12H), 0.86 (t, \(J = 7.2\) Hz, 6H).

\(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 160.7, 150.3, 138.6, 125.0, 117.8, 42.2, 40.1, 32.9, 32.0, 29.8, 26.6, 25.8, 22.8, 14.2, 10.8.

HRMS (ESI\(^+\)): \(m/z\) calcd. for C\(_{15}\)H\(_{25}\)BrN ([M+H\(^+\)]) 298.11649, found 298.11762

Chiral SFC: (216 nm, Phenomenex Lux Amylose-1 (3.0 x 150 mm; 3μm), Mobile phase A: CO\(_2\) Mobile phase B: Methanol (linear gradient from 98:02 to 90:10 in 3 min. then flush with 60:40, 40 °C, Pump Flow: 1.0ml/min), \(t_R\) = 1.99 min (major), \(t_R\) = 2.11 min (minor)

\((S)-4-(2\text{-phenylpentyl})pyridine\) (16a)

[Image of (S)-4-(2-phenylpentyl)pyridine]

The reaction was performed using general procedure A, with 0.1 mmol \(12a\), TMSOTf (0.3 mmol, 3.0 equiv), \(n\)-PrMgCl (2M in Et\(_2\)O, 0.3 mmol, 3.0 equiv), CuBr·SMe\(_2\) (0.01 mmol, 10 mol\%), ligand \((R,S_p)-L1\) (0.012 mmol, 12 mol\%) in 1mL DCM. Product 16a was obtained as pale-yellow oil after flash-column chromatography (SiO\(_2\), pentane:EtOAc 80:20, v/v), [75\% yield, 93\% ee]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.39 (s, 2H), 7.28 – 7.20 (m, 2H), 7.20 – 7.13 (m, 1H), 7.10 – 7.02 (m, 2H), 6.91 (d, \(J = 5.3\) Hz, 2H), 2.93 – 2.77 (m, 3H), 1.69 – 1.59 (m, 2H), 1.28 – 1.10 (m, 2H), 0.83 (t, \(J = 7.3\) Hz, 3H).

\(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 149.8, 149.5, 144.2, 128.5, 127.8, 126.4, 124.7, 47.1, 43.2, 38.3, 20.7, 14.1.

HRMS (ESI\(^+\)): \(m/z\) calcd. for C\(_{16}\)H\(_{20}\)N ([M+H\(^+\)]) 226.15903, found 226.15897

CSP-HPLC: (254 nm, Chiralcel OZ-H, \(n\)-heptane:iPrOH = 98:02, 40 °C, 0.5 ml/min.), \(t_R\) = 29.04 min (major), \(t_R\) = 31.39 min. (minor)

\((S)-4-(2\text{-phenyloctyl})pyridine\) (16b)

[Image of (S)-4-(2-phenyloctyl)pyridine]

The reaction was performed using general procedure A, with 0.1 mmol \(12a\), TMSOTf (0.3 mmol, 3.0 equiv), \(n\)-HexylMgBr (2M in Et\(_2\)O, 0.3 mmol, 3.0 equiv), CuBr·SMe\(_2\) (0.01 mmol, 10 mol\%), ligand \((R,S_p)-L1\) (0.012 mmol, 12 mol\%) in 1mL DCM. Product 16b was obtained as pale-yellow oil after flash-column chromatography (SiO\(_2\), pentane:EtOAc 85:15 → 80:20, v/v), [81\% yield, 95\% ee]
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.39 (s, 2H), 7.23 (d, $J = 7.5$ Hz, 2H), 7.20 – 7.13 (m, 1H), 7.08 – 7.01 (m, 2H), 6.90 (d, $J = 5.3$ Hz, 2H), 2.96 – 2.71 (m, 3H), 1.65 (q, $J = 7.2$, 6.4 Hz, 2H), 1.38 – 1.04 (m, 8H), 0.83 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 149.8, 149.5, 144.3, 128.4, 127.8, 126.4, 124.7, 47.4, 43.2, 36.1, 31.8, 29.4, 27.6, 22.7, 14.2.

HRMS (ESI$^+$): $m/z$ calcd. for C$_{19}$H$_{26}$N ([M+H$^+$]) 268.20598, found 268.20666

CSP-HPLC: (254 nm, Chiralcel OZ-H, n-heptane:iPrOH = 97:03, 40 °C, 0.5 ml/min.), $t_R = 18.40$ min (major), $t_R = 19.47$ min. (minor)

(5)-4-(5-methyl-2-phenylhexyl)pyridine (16c)

The reaction was performed using general procedure A, with 0.1 mmol 12a, TMSOTf (0.3 mmol, 3.0 equiv), i-PentylMgBr (2M in Et$_2$O, 0.3 mmol, 3.0 equiv), CuBr·SMe$_2$ (0.01 mmol, 10 mol%), ligand (R,S)$^-$$^-$L1 (0.012 mmol, 12 mol%) in 1mL DCM. Product 16c was obtained as pale-yellow oil after flash-column chromatography (SiO$_2$, pentane:EtOAc, 90:10, v/v), [65% yield, 97% ee]

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.38 (d, $J = 6.0$ Hz, 2H), 7.25 – 7.20 (m, 2H), 7.19 – 7.14 (m, 1H), 7.05 (d, $J = 6.8$ Hz, 2H), 6.89 (d, $J = 6.1$ Hz, 2H), 2.96 – 2.70 (m, 3H), 1.72 – 1.60 (m, 2H), 1.47 (hept, $J = 6.7$ Hz, 1H), 1.17 – 0.91 (m, 2H), 0.84 – 0.76 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 149.9, 149.5, 144.3, 128.5, 127.8, 126.4, 124.7, 47.7, 43.2, 36.8, 33.9, 28.2, 22.9, 22.5.

HRMS (ESI$^+$): $m/z$ calcd. for C$_{18}$H$_{24}$N ([M+H$^+$]) 254.19033, found 254.19030,

CSP-HPLC: (254 nm, Chiralcel OZ-H, n-heptane:iPrOH = 99:01, 40 °C, 0.5 ml/min.), $t_R = 47.10$ min (major), $t_R = 51.82$ min. (minor)

(S)-4-(2-isobutylloctyl)pyridine (16d)

The reaction was performed using general procedure A, with 0.1 mmol 12d, TMSOTf (0.3 mmol, 3.0 equiv), i-ButylMgBr (2M in Et$_2$O, 0.3 mmol, 3.0 equiv), CuBr·SMe$_2$ (0.01 mmol, 10 mol%), ligand (R,S)$^-$$^-$L1 (0.012 mmol, 12 mol%) in 1mL DCM. Product 16d was obtained as pale-yellow oil after flash-column chromatography (SiO$_2$, pentane:EtOAc 80:20 v/v), [56% yield, 64% ee]

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.48 (s, 2H), 7.07 (d, $J = 5.7$ Hz, 2H), 2.50 (d, $J = 6.9$ Hz, 2H), 1.77 – 1.56 (m, 2H), 1.38–1.08 (m, 11H), 1.08 – 0.97 (m, 1H), 0.91 – 0.83 (m, 6H), 0.81 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 151.0, 149.6, 124.9, 43.4, 40.4, 36.8, 33.5, 32.0, 29.7, 26.4, 25.4, 23.1, 22.8, 14.2.
**HRMS (ESI+):** $m/z$ calcd. for C$_{17}$H$_{30}$N ([M+H$^+$]) 248.23728, found 248.23704

**CSP-HPLC:** (254 nm, Chiralcel OZ-H, n-heptane:iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), $t_R$ = 39.87 min (minor), $t_R$ = 42.18 min. (major)

(R)-4-(2-cyclopentyloctyl)pyridine (16e)

![](image)

The reaction was performed using general procedure A, with 0.1 mmol 12d, TMSOTf (0.3 mmol, 3.0 equiv), cyclopentylMgBr (2M in Et$_2$O, 0.4 mmol, 4.0 equiv), CuBr·SMe$_2$ (0.01 mmol, 10 mol%), ligand (R,S$_p$)-L1 (0.012 mmol, 12 mol%) in 1mL DCM. Product 16e was obtained as pale yellow oil after flash-column chromatography (SiO$_2$, pentane:EtOAc 80:20 v/v), [54% yield, 89% ee]

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.47 (s, 2H), 7.08 (d, $J$ = 4.8 Hz, 2H), 2.77 – 2.34 (m, 2H), 1.94 – 1.38 (m, 8H), 1.38 – 1.10 (m, 12H), 0.86 (t, $J$ = 6.9 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 151.4, 149.6, 124.8, 44.1, 43.2, 38.3, 31.9, 31.0, 30.7, 30.1, 29.8, 26.3, 25.6, 25.6, 22.8, 14.2.

**HRMS (ESI+):** $m/z$ calcd. for C$_{18}$H$_{29}$N ([M+H$^+$]) 260.23728, found 260.23713

**CSP-HPLC:** (254 nm, Chiralcel OJ-H, n-heptane:iPrOH = 99.6:0.4, 40 °C, 0.35 ml/min.), $t_R$ = 12.95 min (major), $t_R$ = 13.86 min. (minor)

(S)-4-(2-ethylhex-5-en-1-yl)pyridine (16f)

![](image)

The reaction was performed using general procedure A, with 0.1 mmol 12d, TMSOTf (0.3 mmol, 3.0 equiv), but-3-en-1-ylMgBr (2M in Et$_2$O, 0.3 mmol, 3.0 equiv), CuBr·SMe$_2$ (0.01 mmol, 10 mol%), ligand (R,S$_p$)-L1 (0.012 mmol, 12 mol%) in 1mL DCM. Product 16f was obtained as pale yellow oil after flash-column chromatography (SiO$_2$, pentane:EtOAc 90:10 v/v), [91% yield, 93% ee]

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.47 (d, $J$ = 5.1 Hz, 2H), 7.06 (d, $J$ = 5.4 Hz, 2H), 5.74 (ddt, $J$ = 16.9, 10.1, 6.6 Hz, 1H), 5.07 – 4.82 (m, 2H), 2.52 (d, $J$ = 7.1 Hz, 2H), 2.13 – 1.95 (m, 2H), 1.68 (m, 1H), 1.42 – 1.14 (m, 12H), 0.87 (t, $J$ = 6.8 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 150.8, 149.7, 138.8, 124.8, 114.6, 39.9, 38.5, 33.1, 32.5, 31.9, 31.0, 29.7, 26.5, 22.8, 14.2.

**HRMS (ESI+):** $m/z$ calcd. for C$_{19}$H$_{28}$N ([M+H$^+$]) 246.22163, found 246.22174

**CSP-HPLC:** (215 nm, Chiralcel OD-H, n-heptane:iPrOH = 99.2:0.8, 40 °C, 0.35 ml/min.), $t_R$ = 25.89 min (major), $t_R$ = 26.54 min. (minor)
(S)-4-(2-phenylhept-6-en-1-yl)pyridine (16g)

The reaction was performed using general procedure A, with 0.1 mmol 12a, TMSOTf (0.3 mmol, 3.0 equiv), pent-4-en-1-ylMgBr (1.8M in Et₂O, 0.3 mmol, 3.0 equiv), CuBr·SMe₂ (0.01 mmol, 10 mol%), ligand (R,S₆)-L₁ (0.012 mmol, 12 mol%) in 1mL DCM. Product 16g was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc, 90:10, v/v), [66% yield, 90% ee]

¹H NMR (400 MHz, CDCl₃) δ 8.41 (s, 2H), 7.31 – 7.20 (m, 2H), 7.21 – 7.12 (m, 1H), 7.06 (d, J = 6.8 Hz, 2H), 6.91 (s, 2H), 5.70 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.00 – 4.80 (m, 2H), 2.97 – 2.72 (m, 3H), 2.10 – 1.89 (m, 2H), 1.73 – 1.56 (m, 2H), 1.36 – 1.17 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 149.7, 149.6, 144.0, 138.7, 128.5, 127.8, 126.5, 124.7, 114.7, 47.3, 43.2, 35.5, 33.8, 26.9.

HRMS (ESI⁺): m/z calcd. for C₁₈H₂₂N ([M+H⁺]) 252.17468, found 252.17467

CSP-HPLC: (254 nm, Chiralcel OZ-H, n-heptane:iPrOH = 99:1.0, 40 °C, 0.5 ml/min.), tᵣ = 51.93 min (major), tᵦ = 56.29 min. (minor)

(S)-4-(2-phenethyloctyl)pyridine (16h)

The reaction was performed using general procedure A, with 0.1 mmol 12d, TMSOTf (0.3 mmol, 3.0 equiv), phenethylMgBr (2.6 M in Et₂O, 0.3 mmol, 3.0 equiv), CuBr·SMe₂ (0.01 mmol, 10 mol%), ligand (R,S₆)-L₁ (0.012 mmol, 12 mol%) in 1mL DCM. Product 16h was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc, 90:10 v/v), [89% yield, 97% ee]

¹H NMR (400 MHz, CDCl₃) δ 8.47 (d, J = 6.0 Hz, 2H), 7.35 – 7.21 (m, 2H), 7.22 – 7.14 (m, 1H), 7.12 (d, J = 6.7 Hz, 2H), 7.05 (d, J = 6.0 Hz, 2H), 2.74 – 2.48 (m, 3H), 1.75 – 1.66 (m, 2H), 1.57 (dq, J = 9.8, 6.4 Hz, 2H), 1.41 – 1.16 (m, 1H), 0.88 (t, J = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 150.7 149.6, 142.5, 128.5, 128.4, 125.9, 124.8, 40.0, 38.6, 35.1, 33.2, 33.1, 32.0, 29.7, 26.5, 22.8, 14.2.

HRMS (ESI⁺): m/z calcd. for C₂₁H₃₆N ([M+H⁺]) 296.23728, found 296.23820

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane:iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), tᵣ = 78.87 min (major), tᵦ = 87.78 min. (minor)
(R)-4-(2-methyloctyl)pyridine (16i)

The reaction was performed using general procedure A, (reaction was carried out at 0°C for 5h, MeMgBr was diluted to 0.5 mL total volume and added to reaction mixture by syringe pump for 30 min) with 0.1 mmol 12d, TMSOTf (0.3 mmol, 3.0 equiv), MeMgBr (3 M in Et2O, 0.3 mmol, 3.0 equiv), CuBr·SMe2 (0.01 mmol, 10 mol%), ligand (R,S)-L1 (0.012 mmol, 12 mol%) in 1mL DCM. Product 16i was obtained as pale-yellow oil after flash-column chromatography (SiO2, pentane:EtOAc, 90:10 v/v), [50% yield, 93% ee] 1H NMR (400 MHz, CDCl3) δ 8.47 (d, J = 5.1 Hz, 2H), 7.07 (d, J = 6.0 Hz, 2H), 2.67 – 2.30 (m, 2H), 1.74 (h, J = 7.2 Hz, 1H), 1.40 – 1.09 (m, 10H), 0.87 (t, J = 6.8 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H).

13C NMR (101 MHz, CDCl3) δ 150.9, 149.5, 124.8, 43.1, 36.8, 34.5, 32.0, 29.6, 27.1, 22.8, 19.5, 14.2.

HRMS (ESI+): m/z calcd. for C14H24N ([M+H+]) 206.19033, found 206.19015

CSP-HPLC: (254 nm, Chiralcel OB-H, n-heptane:iPrOH = 99.8:0.2, 40 °C, 0.5 ml/min.), tR = 10.22 min (major), tR = 10.59 min. (minor)

(R)-4-(2-phenyloctyl)pyridine (16j)

The reaction was performed using general procedure A, with 0.1 mmol 12d, TMSOTf (0.3 mmol, 3.0 equiv), phenylMgBr (3 M in Et2O, 0.3 mmol, 3.0 equiv), CuBr·SMe2 (0.01 mmol, 10 mol%), ligand (R)-L10 (0.012 mmol, 12 mol%) in 1mL DCM. Product 16j was obtained as pale-yellow oil after flash-column chromatography (SiO2, pentane:EtOAc, 97:03 v/v), [84% yield, 0% ee] 1H NMR (400 MHz, CDCl3) δ 8.38 (d, J = 5.5 Hz, 2H), 7.27 – 7.19 (m, 2H), 7.17 (d, J = 7.2 Hz, 1H), 7.08 – 7.02 (m, 2H), 6.90 (d, J = 6.0 Hz, 2H), 2.95 – 2.73 (m, 3H), 1.72 – 1.59 (m, 2H), 1.28 – 1.10 (m, 8H), 0.83 (t, J = 6.9 Hz, 3H).

13C NMR (101 MHz, CDCl3) δ 150.9, 149.5, 144.2, 128.4, 127.8, 126.4, 124.7, 47.4, 43.2, 36.1, 31.8, 29.4, 27.6 22.7, 14.2.

HRMS (ESI+): m/z calcd. for C19H26N ([M+H+]) 268.20598, found 268.20686

CSP-HPLC: (206 nm, Chiralcel OZ-H, n-heptane:iPrOH = 97:03, 40 °C, 0.5 ml/min.), tR = 18.39 min, tR = 19.39 min.

4.4.7 Controlled Experiments

a) Procedure for reaction at room temperature: In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, was added CuBr·SMe2 (0.01 mmol, 0.1 equiv) and ligand L1 (0.012 mmol, 0.12 equiv) dissolved in DCM (0.7 mL) and stirred at RT under nitrogen atmosphere for 15 min. The substrate 12a (0.1 mmol, 1.0 equiv) was added at once using 0.3 mL DCM and stirred for 5 min. To the resulting reaction mixture, at RT, TMSOTf (0.3 mmol,
3.0 equiv) was added. After stirring for 5 min. EtMgBr (0.3 mmol, 3.0 equiv, diluted total volume of 1 mL in Et₂O) was added by syringe pump for 30 min. Reactions was quenched after stirring for additional 5 min. and the product 13a was isolated as in general procedure A. [91% yield, 79% ee]

b) Procedure for reaction at 0 °C: In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, was added CuBr·SMe₂ (0.01 mmol, 0.1 equiv) and ligand L₁ (0.012 mmol, 0.12 equiv) dissolved in DCM (0.7 mL) and stirred at RT under nitrogen atmosphere for 15 min. The substrate 12a (0.1 mmol, 1.0 equiv) was added at once using 0.3 mL DCM and stirred for 5 min. Reaction mixture cooled to 0 °C and TMSOTf (0.3 mmol, 3.0 equiv) was added. After stirring for 5 min. EtMgBr (0.3 mmol, 3.0 equiv, diluted total volume of 1 mL in Et₂O) was added by syringe pump for 30 min. Reactions was quenched after stirring for additional 5 min. and the product 13a was isolated as in general procedure A. [96% yield, 83% ee]

c) Procedure for large-scale reaction and recovery of chiral catalyst: Large scale reaction was performed using general procedure A, with only difference of reaction scale (0.1 mmol vs 3.0 mmol). After usual workup, catalyst was isolated in the form of complex by column chromatography (SiO₂, pentane:EtOAc, 80:20 v/v). [recovered yield of complex = 81%; yield of product = 94%, ee = 94%].

d) Procedure for reuse of chiral catalyst: In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, the recovered complex (0.01 mmol, 0.1 equiv) from above reaction was dissolved in DCM (0.7 mL) and stirred under nitrogen atmosphere for 15 min. The substrate 12a (0.1 mmol, 1.0 equiv) was added at once using 0.3 mL DCM. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C and TMSOTf (0.3 mmol, 3.0 equiv) was added followed by EtMgBr (0.3 mmol, 3.0 equiv). After stirring at -78 °C for 16h, the reaction was quenched and product 13a was isolated as in general procedure A. [93% yield, 88% ee]

4.4.8 Synthesis and Characterization of Functionalized Pyridines (17-21).

(S)-4-(2-phenylbutyl)piperidine (17)
**Procedure:** A 4 mL glass vial with a magnetic stirring bar was charged with 5% Palladium on carbon (35 mg, approx. 0.016 mmol, 0.07 equiv), chiral pyridine derivative 13a (50 mg, 0.23 mmol, 1 equiv) and AcOH (0.5 mL). The vial is placed in a 5 mL high-pressure autoclave, closed, and evacuated with hydrogen 3-times. The autoclave was charged with 30 bars of hydrogen and kept stirring for 16 h at 80 °C. After cooling, hydrogen gas was carefully released, vial was removed from autoclave, and reaction mixture was transfer to a pad of celite and washed several times with EtOAc. Collected fractions were dried on rotary evaporator, dissolved in 1 mL of EtOAc and passed through a small pad of alumina in Pasteur pipette, flushed with EtOAc. Volatiles were removed on rotary evaporator to obtained almost clean product 17 as clear oil (49 mg, quantitative yield).

**1H NMR** (400 MHz, CDCl₃) δ 7.32 – 7.24 (m, 2H), 7.21 – 7.15 (m, 1H), 7.14 – 7.10 (m, 2H), 3.04 – 2.90 (m, 2H), 2.59 – 2.37 (m, 3H), 1.81 – 1.67 (m, 4H), 1.67 – 1.42 (m, 4H), 1.14 – 0.96 (m, 1H), 0.74 (t, J = 7.4 Hz, 3H).

**13C NMR** (101 MHz, CDCl₃) δ 145.9, 128.3, 127.8, 125.9, 46.8, 46.8, 44.4, 44.3, 34.6, 33.7, 33.4, 30.4, 12.3.

**HRMS (ESI+):** m/z calcd. for C₁₅H₂₄N ([M+H⁺]) 218.19033, measured mass:218.19026

(R)-2-(2-ethylcloxyl)-5-(1H-tetrazol-5-yl)pyridine (18)

**Procedure:** A heat dried Schlenk tube equipped with glass stopper and magnetic stirring bar was charged under nitrogen with, chiral pyridine derivative 15g (24.4 mg, 1 equiv), sodium azide (19.5 mg, 0.3 mmol, 3 equiv), ammonium chloride (16.1 mg, 0.3 mmol, 3 equiv) and suspended in 1.5 mL of dry DMF. The Schlenk was closed under nitrogen and kept stirring at 90 °C for 20 h. After cooling to room temperature was added 2N HCL (1 mL) and H₂O (1 mL), then carefully neutralizes to pH 7 by adding NaOH solution and extracted with EtOAc (10 mL × 3). Combined organic phases were dried over Na₂SO₄, filtered and volatiles were removed on rotary evaporator. The oily crude was purified by flash-column chromatography, non-polar impurities were removed by flushing with mixture of pentane:EtOAc (80:20) and product was eluted with EtOAc. Volatiles were removed on rotary evaporator and product 18 was isolated as oil (23.8 mg, 82% yield).

**1H NMR** (400 MHz, CDCl₃) δ 9.65 (s, 1H), 9.44 (s, 1H), 8.59 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 2.90 (d, J = 7.3 Hz, 2H), 1.96 – 1.77 (m, 1H), 1.36 – 1.09 (m, 12H), 0.93 – 0.72 (m, 6H).

**13C NMR** (101 MHz, CDCl₃) δ 163.2, 157.3, 145.7, 136.9, 125.2, 121.8, 41.8, 40.5, 32.9, 31.9, 29.7, 26.6, 25.7, 22.7, 14.2, 10.7.
**HRMS (ESI\(^+\))**: m/z calcd. for C\(_{16}H_{26}N_5\) ([M+H\(^+\)]\(^\bullet\)) 288.21827, found 288.21844

**Ethyl (R,E)-3-(6-(2-ethyloctyl)pyridin-3-yl)acrylate (19)**

![Chemical Structure](image)

**Procedure**: A heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar was charged under nitrogen with, Pd(OAc)\(_2\) (2.8 mg, 0.0125 mmol, 0.05 equiv) and Tri(p-tolyl)phosphine (9.5 mg, 0.0315 mmol, 0.125 equiv), dissolved in N-methylpyrrolidinone (1mL) and added ethyl acrylate (345 mg/ 375 µL, 0.86 mmol, 3.5 equiv). The resulting reaction mixture was evacuated 3-times by vacuum-nitrogen cycle, and heated to 90 °C under nitrogen atmosphere for 15 minutes. To this mixture was added triethylamine (94 µL, 0.675 mmol, 2.7 equiv) and a chiral pyridine derivative 15i (75 mg, 0.25 mmol, 1 equiv) in 1 mL n-methylpyrrolidinone dropwise. Rubber septum was quickly replaced with glass stopper and reaction kept stirring at 102 °C overnight (17h). After cooling, 1 mL water was added followed by 5 mL EtOAc and filtered through a pad of celite, washed several times with water and EtOAc. Organic phase was separated and aqueous phase was extracted twice with EtOAc (10 mL). Combined organic phases were dried over MgSO\(_4\), filtered and volatiles were evaporated on rotary evaporator. The resulting oily crude was purified by flash-column chromatography (SiO\(_2\), Pentane:EtOAc 96:4, v/v). The product 19 was isolated as pale-yellow oil (59 mg, 70% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.63 (d, \(J = 2.2\) Hz, 1H), 7.71 (dd, \(J = 8.1, 2.3\) Hz, 1H), 7.64 (d, \(J = 16.1\) Hz, 1H), 7.13 (d, \(J = 8.1\) Hz, 1H), 6.44 (d, \(J = 16.0\) Hz, 1H), 4.25 (q, \(J = 7.1\) Hz, 2H), 2.71 (d, \(J = 7.2\) Hz, 2H), 1.81 (hept, \(J = 6.0\) Hz, 1H), 1.32 (t, \(J = 7.2\) Hz, 3H), 1.31 – 1.15 (m, 12H), 0.90 – 0.74 (m, 6H).

\(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.6, 164.2, 149.4, 141.2, 134.2, 127.5, 123.8, 119.3, 60.8, 42.8, 40.1, 33.0, 32.0, 29.7, 28.9, 26.6, 25.8, 14.4, 14.2, 10.8.

**HRMS (ESI\(^+\))**: m/z calcd. for C\(_{20}H_{32}NO_2\) ([M+H\(^+\)]\(^\bullet\)) 318.24330, found 318.24289
Product 20 was prepared by literature procedure.9

**Procedure:** In a flame dried Schlenk solution of compound 15i (29.8 mg, 0.1 mmol, 1.0 equiv, in 0.2 ml of THF) is added and cooled to 0 °C followed by dropwise addition of BF₃·OEt₂ (14 μl, 0.11 mmol, 1.1 equiv) and stirred for 30 minutes. The reaction mixture is cooled to -50 °C and iPrMgCl·LiCl (1.3M in THF, 100 μl, 0.13 mmol, 1.3 equiv) is added dropwise. The reaction mixture is allowed to stir at the same temperature for 2 h. Chloranil (49.2 mg, 0.2mmol, 2.0 equiv) was added next and the reaction was warmed to RT and stirred overnight. The reaction was quenched with 3M solution of NaOH (1ml) and extracted with diethyl ether (5 mL × 3). Combined organic phases were dried on MgSO₄, filtered, and volatiles were removed on rotary evaporator to obtain oily crude, which was purified by flash-column chromatography (pentane:EtOAc 99:1) to obtain heteroaryl product 20 as pale-yellow oil (17.3 mg, 51% yield)

**1H NMR** (400 MHz, CDCl₃) δ 8.53 (s, 1H), 6.99 (s, 1H), 3.27 (hept, J = 6.9 Hz, 1H), 2.74 – 2.54 (m, 2H), 1.88 – 1.70 (m, 1H), 1.44 – 1.04 (m, 18H), 0.94 – 0.81 (m, 6H).

**13C NMR** (101 MHz, CDCl₃) δ 161.2, 155.7, 151.2, 121.9, 119.9, 42.3, 40.0, 32.9, 32.6, 32.0, 29.8, 26.6, 25.9, 22.8, 22.1, 14.2, 10.9.

**HRMS (ESI-):** m/z calcd. for C₁₈H₃₁BrN ([M+H⁺]) 340.16344, found 340.16361

(R)-2-(2-ethyloctyl)-4-isobutoxy-5-(trifluoromethyl)pyridine (21)

Product 21 was prepared in 2-steps by modifying literature procedure.16
**Step-I. Preparation of phosphonium salt:** A heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar was charged under nitrogen with, chiral pyridine derivative **15e** (50 mg, 0.17 mmol, 1 equiv) in 1 mL DCM. The reaction mixture was cooled to -78 °C and Tf$_2$O (49.1 mg/approx. 30 µL, 0.17 mmol, 1 equiv) was added dropwise. The reaction was stirred for 30 minutes and PPh$_3$ (49.1 mg, 0.187 mmol, 1.1 equiv) in 0.5 mL DCM was added. The reaction was stirred for a further 30 minutes at -78 °C, and organic base 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (26.5 mg/approx 26 µL, 0.17 mmol, 1 equiv) was added. The resulting reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched by adding 1 mL H$_2$O. The mixture was diluted with DCM and H$_2$O, the resulting organic phase was removed and washed three times with H$_2$O. The organic layer was dried over MgSO$_4$, filtered and volatiles were removed on rotary evaporator. The resulting crude was analysed by NMR which showed 76 % conversion towards phosphonium salt. The crude was used in next step without further purification.

**Step-II. Preparation of heteroaryl ether:** A heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar was charged under nitrogen with, sodium hydride (60% dispersion in mineral oil, 10.2 mg, 0.25 mmol, 1.5 equiv) and 1 mL THF. Cooled to 0 °C and 2-methylpropan-1-ol (23.5 µL, 0.25 mmol, 1.5 equiv) was added dropwise. The reaction was stirred for 30 minutes and the crude phosphonium salt from step-I (1.0 equiv) in 0.5 mL THF was added in one portion. The ice bath was removed and the reaction stirred for 15 hours while warming to room temperature. The reaction was quenched by adding 1 mL H$_2$O, diluted by DCM and H$_2$O, the aqueous phase was separated and extracted with DCM three times. The combined organic phases were washed with brine, dried over MgSO$_4$, filtered and volatiles were removed on rotary evaporator. The residue was purified by flash-column chromatography (pentane:EtOAc 99:1) to obtain heteroaryl ether product **21** as pale-yellow oil (38.8 mg, 63% yield).

**$^1$H NMR (400 MHz, CDCl$_3$) δ 8.55 (s, 1H), 6.67 (s, 1H), 3.84 (d, $J = 6.2$ Hz, 2H), 2.69 (d, $J = 7.2$ Hz, 2H), 2.23 – 2.06 (m, $J = 6.6$ Hz, 1H), 1.93 – 1.73 (m, 1H), 1.41 – 1.12 (m, 12H), 1.05 (d, $J = 6.7$ Hz, 6H), 0.94 – 0.77 (m, 6H).

**$^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.4 , 163.3 (h, $J = 2.5$, 1.3 Hz), 147.5 (q, $J = 5.6$ Hz), 123.6 (q, $J = 272.2$ Hz), 113.1 (q, $J = 31.0$ Hz), 107.2 , 74.8 , 43.4 , 39.9 , 32.9 , 32.0 , 29.8 , 28.2 , 26.6 , 25.8 , 22.8 , 19.0 , 14.2 , 10.8.

**HRMS (ESI+):** $m/z$ calcd. for C$_{20}$H$_{33}$F$_3$NO ([M+H$^+$]) 360.25088, found 360.25194

**CSP-HPLC:** (254 nm, Chiralcel OB-H, n-heptane:iPrOH = 99.8:0.2, 40 °C, 0.5 ml/min.), $t_R$ = 19.61 min (major), $t_R$ = 20.72 min. (minor).
4.4.9 Synthesis and Characterization of Cu-Complexes Derived From Ligand L7 and L8

(R)-1-[(S)p]-2-(Dicyclohexylphosphino)ferrocenyl-ethyl-di[3,5-bis-(trifluoromethyl)phenyl] phosphine-Cu complex (Cu-L7)

Copper complex Cu-L7 was synthesized according to the literature procedure. The analytical data were found to be in accordance with those reported in the literature.

\[ ^1H\text{ NMR (CDCl}_3, 400\text{ MHz): } \delta \begin{array}{l} 8.28 (s, 2H), 7.89 (s, 2H), 7.85 (s, 1H), 7.37 (s, 1H), 4.30 (s, 1H), 4.23 (s, 1H), 4.18 (s, 5H), 4.12 (s, 1H), 3.86 (q, 1H), 1.0-2.0 (m, 25H). \end{array} \]

\[ ^{31}P\text{ NMR (CDCl}_3, 161.94\text{ MHz): } \delta \begin{array}{l} 14.31 (\text{br. d, } J = 155.3 \text{ Hz}), \end{array} \]

\[ ^{19}F\text{ NMR (CDCl}_3, 376.29\text{ MHz): } \delta \begin{array}{l} -63.1. \end{array} \]

(R)-1-[(S)p]-2-(Dicyclohexylphosphino)ferrocenyl-ethyl-di(3,5-xylyl)phosphine-Cu complex (Cu-L8)

Copper complex Cu-L8 was synthesized according to the literature procedure.

\[ ^1H\text{ NMR (CDCl}_3, 400\text{ MHz): } \delta \begin{array}{l} 7.33 (d, J = 9.2 \text{ Hz, } 2H), 7.16 (d, J = 9.1 \text{ Hz, } 2H), 6.97 (s, 1H), 6.89 (s, 1H), 4.33 (s, 1H), 4.29 (s, 1H), 4.21 (s, 1H), 4.02 (s, 5H), 3.57 (m, 1H), 2.57 (m, 1H), 2.29 (s, 6H), 2.19 (s, 6H), 2.03 – 0.87 (m, 25H). \end{array} \]

\[ ^{13}C\text{ NMR (CDCl}_3, 100.58\text{ MHz): } \delta \begin{array}{l} 138.1 (d, J = 9.3 \text{ Hz}), 137.7 (d, J = 9.6 \text{ Hz}), 132.5 (dd, J = 19.0, 8.2 \text{ Hz}), 132.0 (d, J = 16.2 \text{ Hz}), 131.8, 131.6 (d, J = 16.4 \text{ Hz}), 131.6 , 130.1 (m), 128.7, 125.6, 93.6 (d, J = 24.4 \text{ Hz}), 74.4 (d, J = 18.6 \text{ Hz}), 73.4, 68.9, 39.4 (dd, J = 11.0, 5.7 \text{ Hz}), 35.5 (m), 33.7 (d, J = 11.1 \text{ Hz}), 31.8 (d, J = 10.9 \text{ Hz}), 30.3 (dd, J = 14.3, 6.7 \text{ Hz}), 29.8 , 28.1 (d, J = 16.5 \text{ Hz}), 27.3 (d, J = 8.4 \text{ Hz}), 26.8 (d, J = 12.3 \text{ Hz}), 26.1 (d, J = 25.5 \text{ Hz}), 24.3, 21.4 (d, J = 19.8 \text{ Hz}), 18.6. \end{array} \]

\[ ^{31}P\text{ NMR (CDCl}_3, 161.94\text{ MHz): } \delta \begin{array}{l} 13.47. \end{array} \]

HRMS (ESI⁺): \( m/z \text{ calcd. for C}_{40}\text{H}_{52}\text{BrCuFeP}_2([M+H⁺]) 792.13676, \text{ found 792.13707} \)
4.4.10 Determination of Absolute Configuration by X-Ray Analysis of 2a’

The absolute configurations of products were determined on the basis of single-crystal X-ray diffraction analysis of compound 13a’ derived from 13a and the stereochemistry was assign to be ‘S’.¹⁸

![X-ray crystal structure of compound 13a’](image)

**Figure S1.** X-ray crystal structure of compound 13a’

A single crystal of compound 13a’ was mounted on top of a cryoloop and transferred into the cold nitrogen stream (100 K) of a Bruker-AXS D8 Venture diffractometer. Diffraction data were collected using Cu Kα radiation; the acquisition strategy was chosen such that a high multiplicity of observations (MoO) was obtained (~ 8) in order to determine the absolute configuration with a reasonable level of certainty. Data collection and reduction was done using the Bruker software suite APEX2.¹⁹ The final unit cell was obtained from the xyz centroids of 9970 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 SHELXT¹⁰ and refinement of the structure was performed using SHELXL.¹¹ Refinement was frustrated by a disorder problem: the pyridinium ring appeared to be disordered over two positions. This was modeled using a two-site occupancy model for which the s.o.f. of the major fraction refined to 0.56. When allowed to refine freely, several atoms in the disordered region resulted in non-positive definite displacement parameters, and ultimately DELU/SIMU instructions were applied. 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. In the final stages of refinement, the Flack x parameter (0.064(4) using Parsons’ method) indicated that the corrected handedness was 118
chosen (refinement of the inverted structure suggested this model was wrong). Crystal data and details on data collection and refinement are presented in Table S1.
Table S1. Crystallographic data for 13a’

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4.5 Bibliography


[18] 13a' was prepared by bubbling HCl gas to the solution of 13a in diethyl ether. Obtained precipitate was isolated by evaporating diethyl ether. Recrystallization was carried out in EtOAc and heptane.
