Copper-catalyzed enantioselective conjugate addition of Grignard reagent to non-activated acceptors
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Chapter 2: Lewis acid enabled copper-catalyzed asymmetric synthesis of chiral β-substituted amides

In this chapter a general methodology for enantioselective conjugate addition of Grignard reagents to simple α,β-unsaturated carboxamides is described. Lewis acids were used to activate the substrates by binding to the carbonyl moiety of amide and thus significantly enhance the electrophilicity of the adjacent olefinic group toward nucleophilic addition. By combining with copper-catalysis, this strategy allowed us to solve the long standing problem of synthesis of chiral β-substituted carboxamides and resulted in methodology that delivers products in excellent yields and enantioselectivities.

Part of this chapter has been published:

2.1 Introduction

Deemed one of the most important structural motifs in organic chemistry, amides are found in a plethora of natural products and bioactive compounds, such as proteins and pharmaceuticals.\textsuperscript{1-4} However, despite almost 80 years of intensive research in the field of copper promoted CA reactions, a general solution for catalytic ACA to simple $\alpha\beta$-unsaturated amides ($\alpha\beta$-unsaturated carboxamides) has not been found.\textsuperscript{5-12} The challenges associated with asymmetric conjugate addition (ACA) to $\alpha\beta$-unsaturated amides are due to the sluggish resonance activation of the olefin moiety via the adjacent carboxamide group (Figure 1a). The high degree of nitrogen lone-pair delocalization, resulting from the orbital overlap with the antibonding orbital of the carbonyl group, makes carboxamide the least electron-deficient carboxylic acid derivative.\textsuperscript{13} Thus, contrary to aldehydes, ketones, and esters, the lowest unoccupied molecular orbital (LUMO) of the corresponding $\alpha\beta$-unsaturated carboxamides is not sufficiently enhanced toward nucleophilic addition at the $\beta$-position.

As a result of this low reactivity, addition of hard organometallics was only possible at temperatures above $-78 \, ^\circ\text{C}$, at which non-catalyzed blank reactions outcompete the catalytic enantioselective pathway. Therefore, the only reported examples of catalytic ACA to simple $\alpha\beta$-unsaturated carboxamides are confined to Rh-catalyzed arylations that do not suffer from non-catalyzed additions at high temperatures.\textsuperscript{14-20} The challenge faced in the development of efficient and stereoselective alkylations of simple $\alpha\beta$-unsaturated carboxamides has led to the development of several alternative approaches, with the most common ones based on specific carboxamide substrates activated by placing an electron-
withdrawing group at the \(N\)-atoms (Figure 1b) to allow electronic activation and/or bidentate coordination with the chiral catalyst.\(^{14-25}\)

Another non-direct method to \(\beta\)-substituted chiral amides is based on 1,4-addition to \(\alpha,\beta\)-unsaturated esters, followed by quenching of the reaction mixture with the corresponding amines.\(^{26}\) Intriguingly, the only reported direct addition to simple \(\alpha,\beta\)-unsaturated carboxamides makes use of Grignard reagents, but the limited scope of the resulting chiral \(\beta\)-alkyl substituted amides and the modest enantioselectivities led the authors to switch to a chiral auxiliary strategy.\(^{27}\) Thus, despite the advances realized, the conjugate alkylation of unactivated \(\alpha,\beta\)-unsaturated carboxamides still constitutes a daunting, so far unsolved, challenge.

Whereas the resonance stabilization impedes the reactivity of \(\alpha,\beta\)-unsaturated carboxamides, it also gives rise to a pronounced Lewis basicity of the amide carbonyl oxygen atom. We hypothesized that coordination of a strong LA to the oxygen atom should significantly enhance the electrophilicity of the adjacent olefinic moiety toward nucleophilic addition thus activating the \(\alpha,\beta\)-unsaturated carboxamides \textit{in situ} (Figure 1c).\(^{28-31}\) This in turn could allow direct additions of hard alkyl nucleophiles, namely Grignard reagents, to simple unactivated \(\alpha,\beta\)-unsaturated carboxamides without the need for specific substrates, while rendering the reaction enantioselective by using chiral catalysts.

2.2 Results and discussions

Table 1: selected optimization data for the Cu-Catalyzed alkylation of carboxamide 1a with EtMgBr\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>L1/Cu(I)</th>
<th>LA</th>
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<th>Conv. [%]</th>
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<td>10</td>
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<td>TMSOTf</td>
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\(^a\)Reaction conditions: 0.1 M of 1a in DCM, LA (2.0 equiv.), EtMgBr (2.0 equiv.). \(^b\)Conversion was determined by \(^1\)H NMR of reaction crude. \(^c\)Enantiomeric excess was determined by HPLC on a chiral stationary phase. Absolute configuration was assigned by analogy with literature data.
We started exploring this concept by evaluating the reactivity of simple trans \(N,N\)-dimethyl \(\alpha,\beta\)-unsaturated carboxamide 1a toward addition of EtMgBr in different reaction conditions. The initial experiments confirmed the inherently poor reactivity of acyclic \(\alpha,\beta\)-unsaturated amides relative to typical Michael acceptors. No addition of the highly reactive EtMgBr to carboxamide 1a was observed when performing the reaction in DCM at \(-78^\circ C\), regardless of whether copper salt or chiral ligand L1 were present (Table 1, entries 1–3). Raising the temperature to 0 \(^\circ C\) resulted in substrate conversion, but unfortunately the reaction with chiral ligand yielded racemic product, and the non-catalyzed reaction was faster than the one promoted by the copper catalyst (Table 1, entries 4–6). At \(-50^\circ C\) the catalyzed reaction rate started to surpass that of the non-catalytic reaction, but still racemic product was obtained (Table 1, entries 7 and 8).

These results indicate that the chiral copper catalyst L1/Cu(I) is not capable of either outcompeting the non-catalyzed racemic addition to simple \(\alpha,\beta\)-unsaturated carboxamides, or of providing CA with enantiodiscrimination. This is a striking difference from the overwhelming literature precedence on Cu-catalyzed asymmetric additions of organometallics to enones and enoates.\(^5\)-\(^11\) At this point we introduced LA to explore the activation of \(\alpha,\beta\)-unsaturated carboxamides toward additions at low temperature (\(-78^\circ C\)).

In the absence of copper salt, no significant amount of product was formed when using BF\(_3\)-Et\(_2\)O. With the more reactive trimethylsilyl trifluoromethanesulfonate (TMSOTf), 50% of product was formed (Table 1, entry 10). However, combining either BF\(_3\)-Et\(_2\)O or TMSOTf with chiral copper catalyst led to an immense acceleration of the ACA reaction. Importantly, apart from outcompeting the non-catalyzed addition of EtMgBr, the catalytic pathway provided the ACA product for the first time with excellent enantioselectivity (Table 1, entries 11 and 12). Further LA, solvent, chiral ligand, and copper salt screening performed using substrate 1b (Table 2) failed to improve these already excellent results, thus establishing the following optimized conditions: 2.0–3.0 equiv. of either of these LAs and 2.0 equiv. of Grignard reagents in the presence of 6 mol% of chiral ligand L1 and 5 mol% of CuBr·SMe\(_2\), with DCM as solvent and in a temperature range from \(-50\) to \(-78^\circ C\). It should be noted that the presence of even traces of THF is detrimental for the reaction conversion and enantioselectivity. Wilhelm Schlenk and Wilhelm Schlenk Jr. proposed ‘Schlenk equilibrium’, namely RMgX is in equilibrium with R\(_2\)Mg and MgX\(_2\).\(^32\) In DCM, only RMgBr is present, which is essential for successful ACA of Grignard reagents. In contrast, when THF is added, the Schlenk equilibrium will shift to the dialkylmagnesium compound.\(^33\) It was shown that dialkylmagnesium compound react at least 10 times faster than the corresponding RMgX, thus significantly accelerating the non-catalyzed racemic reaction.\(^34\) Therefore, Grignard reagents must be used either in Et\(_2\)O or MTBE instead of THF.
Table 2: screening of chiral ligands, solvents, LA for copper 1,4-addition of EtMgBr to acyclic α,β-unsaturated carboxamide 1b
d

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
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<th>Equiv. of LA</th>
<th>Equiv. of EtMgBr</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Yield [%](^d)</th>
<th>ee [%](^c)</th>
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<td>2.0</td>
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<td>−60</td>
<td>57</td>
<td>92</td>
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\(^a\)Reaction conditions: 0.2 mmol of 1b in 2 mL of solvent, CuBr·SMe₂ (5 mol%), ligand L (6 mol%), LA (1.1–2.0 equiv.), EtMgBr (3.0 M in Et₂O, 1.1–2.0 equiv.), T (°C), 18 h. \(^b\)Yield of isolated 2b. \(^c\)Enantiomeric excess was determined by HPLC on a chiral stationary phase. \(^d\)This value is related to the conversion.

With the optimized set of conditions in hand, we investigated the generality of this methodology (Figure 2), testing both BF₃·Et₂O and TMSOTf as LA. Although both LA’s enable ACA to almost all tested α,β-unsaturated carboxamides, TMSOTf generally works best for relatively unreactive and unhindered α,β-unsaturated carboxamides, while BF₃·Et₂O is the LA of choice for relatively reactive, both hindered or unhindered, α,β-unsaturated carboxamides.
Scope of substituents at N-atom of enamides for additions of EtMgBr

2b 79% yield, 94% ee<sup>a</sup>  
2c 52% yield, 98% ee<sup>a</sup>  
2d 78% yield, 97% ee<sup>a</sup>  
2e 72% yield, 97% ee<sup>a</sup>  
2f 66% yield, 77% ee<sup>a</sup>  
2g 83% yield, 86% ee<sup>a,b</sup>  
2h 65% yield, 95% ee<sup>a,c</sup>  
2i 75% yield, 96% ee<sup>a</sup>  
2j 75% yield, 93% ee<sup>a</sup>

Scope of β-substituents of the enamides for additions of EtMgBr

2a 73% yield, 97% ee<sup>a</sup>  
2k 71% yield, 98% ee<sup>a</sup>  
2l 73% yield, 93% ee<sup>a</sup>  
2m 70% yield, 94% ee<sup>a</sup>  
2n 63% yield, 93% ee<sup>a,b</sup>  
2o 81% yield, 96% ee<sup>a</sup>  
2p 67% yield, 90% ee<sup>a,b</sup>  
2q 70% yield, 97% ee<sup>a</sup>  
2r 74% yield, 95% ee<sup>a</sup>  
2s 85% yield, 95% ee<sup>a</sup>  
2t 63% yield, 91% ee<sup>a,b</sup>  
2u 63% yield, 96% ee<sup>a</sup>  
2v 74% yield, 95% ee<sup>a</sup>  
2w 76% yield, 97% ee<sup>a</sup>  
2x 71% yield, 93% ee<sup>a</sup>

Scope of β-substituents of the enamides for additions of EtMgBr

3a 78% yield, 87% ee<sup>a</sup>  
3b 84% yield, 95% ee<sup>a</sup>  
3c 77% yield, 97% ee<sup>a</sup>  
3d 73% yield, 97% ee<sup>a</sup>  
3e 80% yield, 97% ee<sup>a</sup>  
3f 82% yield, 97% ee<sup>a</sup>  
3g 41% yield, 98% ee<sup>a</sup>  
3h 93% yield, 99% ee<sup>a</sup>  
3i 54% yield, 99% ee<sup>a</sup>
Figure 2: product scope of Lewis acid promoted copper-catalyzed ACA methodology. Isolated yields for all the products are shown. Absolute configuration was assigned by analogy with literature data. Reaction conditions: a 2.0−3.0 equiv. of BF$_3$·Et$_2$O were used as LA at −78 °C. In this case 10 mol % of CuBr·SMe$_2$ and 12 mol % of L1 were used. Weinreb amide was used in this case, and it underwent demethoxylation. Without LA at −50 °C, <2.0–3.0 equiv. of TMSOTf was used as LA at −50 °C.

First, we evaluated various substituents at the nitrogen atom and found that a wide variety can be used, allowing efficient transformation to the corresponding β-chiral amides. ACA to N-diallyl, N-dibenzyl, and N-di(p-methoxybenzyl) groups, with possible subsequent deprotection in mind, are well-tolerated and give the corresponding CA products (2c−2e) with good yields and excellent (98%) ee. Addition of EtMgBr to carboxamide with a N-phenyl-N-methyl group led to CA product 2f with 77% ee. Notably, CA to highly activated carboxamide with N-tosyl-N-methyl groups, a substrate that provides the CA product with a dramatic 36% of ee in the absence of a LA, now yielded product 2g with a high ee of 86%. Addition to Weinreb-type carboxamide proceeded with excellent chemo- and enantioselectivity and led to the secondary amide product 2h, resulting from demethoxylation. Gratifyingly, CA to morpholine-substituted carboxamide leading to product 2i, amenable to further synthetic transformations, proceeded with 75% of isolated yield and 96% of ee. Finally, even addition of EtMgBr to the six-membered α,β-unsaturated lactam bearing an endocyclic double bond, resulting in product 2j, succeeded. Interestingly, no Lewis acid was required in this case, most likely due to the higher reactivity of cyclic Michael acceptors toward nucleophiles compared to linear analogues. Carrying out the reaction in the presence of BF$_3$·Et$_2$O or TMSOTf led to side reactions, and the CA product 2j was obtained with an ee of 79% due to the competing background reaction. Low conversions and racemic products were obtained when primary or secondary amides were used as Michael acceptors.

Having established that our catalytic system tolerates a broad scope of variations at the N-atom, we subsequently explored α,β-unsaturated amides with different substitution patterns at the β-position. We were delighted to find that excellent results are obtained with substrates featuring linear as well as branched carbon chains (2a, 2b, 2k, 2l), aromatic rings (2m−2r), heteroaromatic substituents (2s−2v), and functional groups such as halogen and unprotected hydroxyl (2w, 2x).

It should be noted that the reactivity of the chiral copper catalyst was not affected by the presence of heteroatoms. The consistently first-rate enantioselectivities and good to excellent yields observed during these experiments highlight the prominent role of the catalyst and the LA in the CA to unreactive α,β-unsaturated carboxamides.

Next, the scope of the reaction in terms of Grignard reagents was examined. It is remarkable that most of the assessed Grignard reagents were suitable partners for this catalytic system, with the exception of PhMgBr, which provided low conversion and racemic product. The lack of enantiocontrol is due to the slower reductive elimination of Cu from Ar-Cu species as compared to alk-Cu, resulting in a slower copper-catalyzed reaction, which consequently is outcompeted by the direct, non-catalytic addition of PhMgBr. The low conversion obtained with PhMgBr is the direct consequence of its high reactivity, since
this causes the reaction with the LA to be faster than the desired CA. It was particularly gratifying that, where previous reports on additions to conjugated $\alpha,\beta$-unsaturated carboxamides were restricted to arylations, our catalytic system enabled the addition of a wide variety of alkyl Grignard reagents (linear as well as $\alpha$, $\beta$- and $\gamma$-substituted and functionalized) with excellent regio- and enantioselectivities (Figure 2, products 2a, 3a–3g). Because of the utmost synthetic relevance of methylated chiral centers in pharmaceuticals, the addition of MeMgBr deserves a special note. Despite the formidable advances realized in copper-catalyzed additions of organometallics, the methylation of the more reactive $\alpha,\beta$-unsaturated esters is still considered a notoriously difficult transformation.$^{35,36}$ Therefore, we anticipated that the addition of MeMgBr, the least reactive among all alkyl Grignard reagents, to $\alpha,\beta$-unsaturated carboxamides, a substrate far less reactive than ester, would be very challenging. However, to our delight, the addition of this reagent was successful, providing the $\beta$-substituted amide 3h in 50% yield and nearly absolute stereocontrol (99% ee). Remarkably, the yield was greatly improved to 93% by using TMSOTf as LA, while retaining the enantioselectivity of 99% (Figure 2, product 3h).

Tests on the temperature tolerance provided a final testament to the robustness and power of our methodology. High levels of selectivity in the ACA of hard organometallics to Michael acceptors are typically possible at temperatures below 0 °C.$^{35,36}$ From an industrial perspective, this requirement is a major restriction for large-scale applications. To challenge our catalytic system further, we carried out the CA reactions to carboxamide 1a at higher temperatures, using both EtMgBr and the relatively less reactive MeMgBr (Table 3). We were pleased that these experiments produced high levels of regio- and enantioselectivity, unprecedented for hard organometallics under these conditions. The corresponding CA products were obtained with good yields and ees above 90% at 0 °C in case of the addition of EtMgBr and at both 0 and 25 °C for the addition of MeMgBr (Table 3, entries 1–3).

Table 3: temperature dependence and 10 g scale reaction$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>1a [mmol]</th>
<th>L1/Cu(I) [mol%]</th>
<th>R</th>
<th>LA</th>
<th>T [°C]</th>
<th>yield [%]$^b$</th>
<th>ee [%]$^c$</th>
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<td>BF$_3$Et$_2$O</td>
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<td>96</td>
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$^a$Reaction conditions: 0.1 M of 1a in DCM, LA (2.0 equiv.), EtMgBr (2.0 equiv.). $^b$Conversion was determined by $^1$H NMR of reaction crude. $^c$Enantiomeric excess was determined by HPLC on a chiral stationary phase. $^d$With recovered L1/Cu(I) complex.

These results convincingly demonstrate the synergistic power of the chiral copper catalyst and the LA, allowing them to outcompete the non-catalyzed reaction at relatively high
temperatures for this chemistry. The nature of the LA is critical to the success of these reactions at high temperatures, with TMSOTf found to be superior in terms of yield and ee.

This catalytic protocol is scalable and operationally simple, as we corroborated by performing the addition of MeMgBr to carboxamide 1a at 0 °C on a preparative scale (10 g, 71 mmol), using 5 mol % of chiral catalyst L1/Cu(I). Full conversion was reached once the addition of the last reaction component, MeMgBr, to the reaction mixture was completed (within a few minutes). The CA product 3h was obtained with excellent yield and enantioselectivity (Table 3, entry 3) with no need for special equipment. The catalyst was recovered with 80% yield and reused for another ACA reaction with similar performance (Table 3, entry 4).

β-Alkyl-substituted chiral secondary amides as well as β-alkyl substituted chiral amines are interesting synthetic targets as these structures are present in various pharmaceutically active ingredients including Cyclotheonamide E5 and Orbiculamide A, both known for their cytotoxic activities.37-43 Similarly, β-alkyl-substituted chiral amines, and in particular trifluoromethylated ones, are known precursors in the synthesis of leukotriene receptor antagonists used, for instance, to treat asthma.42,43 To showcase the utility of our catalytic protocol, we demonstrated that chiral β-substituted amide 2e can easily be transformed into a number of corresponding valuable molecules (Scheme 1). Deprotection44 of 2e afforded chiral β-ethyl amide 4, which in turn can be used for the synthesis of the chiral γ-ethyl chiral amine 5 via reduction of the carbonyl moiety or to β-ethyl chiral amine 6 through Hofmann rearrangement.45 We have also applied our ACA methodology to the methylation of trifluoromethylated carboxamide 1y, leading to β-methyl-substituted amide product 3j with 99% ee (Scheme 2).

**Scheme 1**: deprotection and further transformations of ACA product 2e. Reaction conditions: (i) in CF3CO2H, reflux, 16 h; (ii) LiAlH4, in THF at 0 °C to 60 °C, 18 h; (iii) C6H5I (5 mol%), m-CPBA, HBF4, in DCM-H2O (95:5) at 25 °C, 48 h, N2.

**Scheme 2**: ACA to trifluoromethylated carboxamide 1y for further applications in the synthesis of a drug candidate. Reaction condition: (i) CuBr·SMe2, L1, BF3·Et2O, MeMgBr, in DCM at −78 °C, 18 h.
When subjected to deprotection and Hofmann rearrangement, this product could lead to a direct precursor of the drug candidate ZENECA ZD 3523\textsuperscript{42,43}. Another synthetically important transformation in which this catalytic system can be engaged is the trapping of the product enolate (Scheme 3). To demonstrate this, we performed the CA reaction to Br-substituted carboxamide \textbf{1w}. When BF\textsubscript{3}-Et\textsubscript{2}O is used as LA, conjugate addition product \textbf{2w} is obtained. However, switching to TMSOTf as LA allows the CA reaction to be followed by intramolecular trapping of the intermediate silyl enolate, providing cyclic product \textit{trans-7} with contiguous stereocenters and as a single diastereoisomer (Figure 3).

\textbf{Scheme 3}: effect of the nature of the LA on the structure of the final ACA product. Reaction conditions: (i) CuBr.SMe\textsubscript{2}, \textbf{L1}, BF\textsubscript{3}-Et\textsubscript{2}O, EtMgBr, in DCM at −78 °C, 18 h; (ii) CuBr.SMe\textsubscript{2}, ligand \textbf{L1}, TMSOTf, EtMgBr, in DCM at −78 °C, 18 h, then RT, 8 h.

\textbf{Figure 3}: \textsuperscript{1}H NMR and 1D NOE experiment of \textit{7}. Selective irradiation on H\textsubscript{1} showed NOE with ethyl moiety (H\textsubscript{6} and H\textsubscript{7}, highlighted) which are positioned on the same side of the ring.

\textbf{2.3 Conclusions}

We have presented a versatile approach to ACA reactions of readily available Grignard reagents to \(\alpha,\beta\)-unsaturated amides, aided by LAs and chiral copper catalysts. The broad scope of substrates as well as Grignard reagents allows even the most challenging and synthetically important methylations to be achieved with good yields and excellent enantioselectivities and makes our methodology by far the most general strategy for CA to carbonyl-based Michael acceptors. The demonstrated temperature tolerance, scalability,
and possibilities for catalyst recovery add to its attractiveness. Several applications have been demonstrated to showcase the usefulness of our methodology.

2.4 Experimental section

2.4.1 General experimental 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. Flash column chromatography was performed using Merck 60 Å 230–400 mesh silica gel. Thin layer chromatography was performed using 0.25 mm E. Merck silica plates (60F-254). Unless otherwise indicated, the products were visualized by UV and KMnO₄ staining. NMR data was collected on Varian VXR400 (¹H at 400.0 MHz; ¹³C at 100.58 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; D₂O, ¹H: 4.79 ppm). Coupling constants are reported in Hertz. Multiplicity is reported with the usual abbreviations (s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet). Exact mass spectra were recorded on a LTQ Orbitrap XL apparatus with ESI ionization. Enantiomeric excess were determined by chiral HPLC analysis using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector.

2.4.2 Chemicals

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 P₂O₅ nitrogen gas. Grignard reagents were purchased from Sigma-Aldrich: EtMgBr, MeMgBr, PhMgBr (3.0 M in Et₂O), i-BuMgBr, i-PentMgBr, n-HexMgBr, c-PentMgBr (2.0 M in Et₂O). All other Grignard reagents were prepared from the corresponding alkyl bromides and Mg activated with I₂ in Et₂O: phenylethylMgBr (2.6 M in Et₂O), pent-4-en-1-ylMgBr (1.7 M in Et₂O) and (4-chlorobutyl)MgBr (1.3 M in Et₂O). All Grignard reagents were titrated by ¹H NMR before use. Unless otherwise noted α,β-unsaturated carboxamides substrates were prepared following the literature methods (*vide infra*). Chiral ligands (L₁–L₄) were purchased from Sigma Aldrich and Solvias. All reported compounds were characterized by ¹H NMR and ¹³C NMR and HRMS techniques.

2.4.3 Determination of absolute configuration

The absolute configuration was determined by comparison of the optical rotation for the compounds 2b ([α]D²⁰ = + 10.4 (c 1.4, CHCl₃), S-configuration) and the ester derived from 2m ([α]D²⁰ = + 16.1 (c 1.43, CHCl₃), S-configuration) with reported data ([α]D²⁰ = − 5.6 (c 1.5, CHCl₃), R-configuration and [α]D²⁰ = + 7.8 (c 1.18, CHCl₃), S-configuration),
The absolute configurations of other compounds were assigned by analogy.

2.4.4 Synthesis of $\alpha,\beta$-unsaturated carboxamides: procedures and characterization of products

The $\alpha,\beta$-unsaturated carboxamides $1a-1x$ were prepared according to the following methods. $1a-1b$, $1f-1j$, $1l-1m$, $1o$, $1q-1s$, $1v$ are known compounds.

**Method 1**

To a cold 0 °C solution of the corresponding carboxylic acid (5 mmol) in DCM (4 mL) was added thionyl chloride (6 mmol) and dry DMF (14 $\mu$L). The solution was then stirred at room temperature for 2 h and concentrated under reduced pressure to remove residual thionyl chloride. The resulting residue was redissolved in DCM (4 mL), cooled at 0 °C and the corresponding amine (8 mmol) was added. Dry triethylamine (6.6 mmol) was added and stirring was continued at ambient temperature (3 h). The solvent was removed under reduced pressure and DCM (14 mL) was added. The organic phase was washed with dilute hydrochloric acid (2.0 M, 2 mL × 2), water (3 mL × 2), and brine (4 mL), and dried over MgSO$_4$. After removal of the solvent, the corresponding $\alpha,\beta$-unsaturated carboxamides were obtained.

**Method 2**

A solution of acyl chloride (0.96 mL, 10 mmol) in 6.3 mL dry Et$_2$O was cooled to 0 °C in an ice-bath. Anhydrous dimethylamine (2.0 M in THF, 10 mL, 20 mmol) was added for over 5 min and the reaction mixture was allowed to warm to room temperature (12 h). The solvents were evaporated under reduced pressure. Product $1b$ was obtained after purification by column chromatography.

**Method 3**

To a cold 0 °C solution of the corresponding acyl chloride (5 mmol) in DCM (4 mL) was added the corresponding amine (8 mmol). Dry triethylamine (6.6 mmol) was added and stirring was continued at ambient temperature (3 h). The solvent was removed under reduced pressure and DCM (14 mL) was added. The organic phase was washed with dilute hydrochloric acid (2.0 M, 2 mL × 2), water (3 mL × 2), and brine (4 mL), and dried over MgSO$_4$. After removal of the solvent, the corresponding $\alpha,\beta$-unsaturated carboxamides were obtained.

**Method 4**

A solution of N-methyl-4-methylbenzenesulfonylamine (1.85 g, 10 mmol) in anhydrous THF (20 mL) cooled at 0 °C was added under nitrogen a solution of n-BuLi (1.6 M in hexanes, 6.9 mL, 11 mmol) and the resulting mixture was stirred for 15 min. Subsequently, crotonyl chloride (1.0 mL, 11 mmol) dissolved in anhydrous THF (5 mL) was added and the mixture was left to warm to room temperature during 2 h. Saturated aqueous NH$_4$Cl solution was added and the mixture was extracted with DCM (14 mL). The organic phase was washed...
with dilute hydrochloric acid (2.0 M, 2 mL × 2), water (3 mL × 2), and brine (4 mL), and dried over MgSO₄. After removal of the solvent, 1g of the product was obtained.

**Method 5**

LDA (1.0 M in THF/hexane, 6.4 mL, 6.4 mmol) was added to a solution of 1-methyl-2-piperidinone (0.66 mL, 5.8 mmol) in 4 mL of THF under nitrogen at −50 °C. After it was stirred at −50 °C for 45 min, the anion solution was transferred into a solution of phenylselenyl chloride (1.22 g, 6.4 mmol) in 4 mL of THF at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 7 h and quenched with water. Then, it was extracted with DCM. The organic layer was then dried (MgSO₄), filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (SiO₂, pentane:Et₂O = 1:2) to afford 1-methyl-3-(phenylseleno)-2-piperidinone (65% yield) as a colorless oil. Then, a solution of m-CPBA (77%, 0.84 g, 3.8 mmol) in anhydrous DCM (10 mL) was added to a solution of 1-methyl-3-(phenylseleno)-2-piperidinone (0.67 g, 2.5 mmol) in anhydrous DCM (10 mL) cooled at 0 °C. The mixture was allowed to rise to room temperature, and stirring was continued for 3 h. Saturated aqueous NaHCO₃ was added, and the aqueous layer was extracted with DCM. The organic layer was then dried (MgSO₄), filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (SiO₂, Et₂O) to afford the corresponding carboxamide 1j (89% yield).

**Method 6**

The corresponding alkene (7.5 mmol) and N,N-dimethylacrylamide (5 mmol) were added simultaneously to a stirred solution of 5 mol% of second generation Grubbs catalyst in DCM (20 mL) at room temperature. The reaction was refluxed under nitrogen for 16 h. The solvent and the remaining N,N-dimethylacrylamide were removed under reduced pressure and the corresponding carboxamide was purified by column chromatography.

**(E)-N,N-Dimethylhex-2-enamide (1a)**

\[
\begin{align*}
\text{O} \\
\text{1a}
\end{align*}
\]

The product 1a was synthesized following Method 1 and obtained as a colorless oil in 86% yield. ¹H NMR (CDCl₃, 400 MHz): δ 6.86 (dt, J = 15.1, 7.0 Hz, 1H, CH=CH), 6.24 (dt, J = 15.1, 1.3 Hz, 1H, CH=CH), 3.07 (s, 3H, NCH₃), 2.99 (s, 3H, NCH₃), 2.23-2.14 (m, 2H, CH₂CH), 1.54-1.43 (m, 2H, CH₂CH₃), 0.93 (t, J = 7.4 Hz, 3H, CH₂CH₃).

**(E)-N,N-Dimethylbut-2-enamide (1b)**

\[
\begin{align*}
\text{O} \\
\text{1b}
\end{align*}
\]
The product 1b was synthesized following Method 2 and obtained as a colorless liquid after column chromatography (SiO$_2$, Et$_2$O) in 90% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 6.87 (dq, $J = 15.0$, 6.9 Hz, 1H, CH=CH), 6.27 (dq, $J = 15.0$, 1.7 Hz, 1H, CH=CH), 3.06 (s, 3H, NCH$_3$), 2.99 (s, 3H, NCH$_3$), 1.87 (dd, $J = 6.9$, 1.7 Hz, 3H, CH$_3$CH).

(E)-N,N-Diallylbut-2-enamide (1c)

The product 1c was synthesized following Method 3 and obtained after column chromatography (SiO$_2$, pentane:Et$_2$O = 2:1) as a colorless oil in 85% of yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 6.93 (dq, $J = 14.9$, 6.9 Hz, 1H, CH$_3$C=), 6.16 (dq, $J = 14.9$, 1.7 Hz, 1H, COCH=), 5.85-5.72 (m, 2H, NCH$_2$CH=), 5.21-5.10 (m, 4H, CH=CH$_2$), 4.01 (d, $J = 5.7$ Hz, 2H, NCH$_2$), 3.91 (d, $J = 4.1$ Hz, 2H, NCH$_2$), 1.86 (dd, $J = 6.9$, 1.7 Hz, 3H, CHCH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 166.7, 142.1, 133.4, 133.1, 121.8, 117.2, 116.7, 49.1, 48.4, 18.3. HRMS (ESI+, m/Z): calcd. for C$_{10}$H$_{16}$NO [M+H]$^+$: 166.1226, found: 166.1224.

(E)-N,N-Dibenzyllbut-2-enamide (1d)

The product 1d was synthesized following Method 3 and obtained after column chromatography (SiO$_2$, pentane:Et$_2$O = 2:1) as a colorless oil in 85% of yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.39-7.17 (m, 10H, CH$_Ar$), 7.08 (dq, $J = 14.9$, 6.9 Hz, 1H, CH$_3$CH=), 6.30 (dq, $J = 14.9$, 1.6 Hz, 1H, COCH=), 4.64 (s, 2H, NCH$_2$), 4.51 (s, 2H, NCH$_2$), 1.87 (dd, $J = 6.9$, 1.6 Hz, 3H, CHCH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 167.4, 143.1, 137.5, 136.9, 129.0, 128.7, 128.4, 127.7, 127.5, 126.6, 121.7, 49.9, 48.5, 18.4. HRMS (ESI+, m/Z): calcd. for C$_{18}$H$_{20}$NO [M+H]$^+$: 266.1539, found: 266.1541.

(E)-N,N-Bis(4-methoxybenzyl)hex-2-enamide (1e)

The product 1e was synthesized following Method 1 and obtained after column chromatography (SiO$_2$, pentane:Et$_2$O = 2:1) as a pale yellow oil in 91% of yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.19 (d, $J = 8.5$ Hz, 2H, CH$_Ar$), 7.09 (d, $J = 8.5$ Hz, 2H, CH$_Ar$), 7.04 (dt, $J = 15.0$, 7.1 Hz, 1H, CH$_2$CH=), 6.89 (d, $J = 8.5$ Hz, 2H, CH$_Ar$), 6.84 (d, $J = 8.5$ Hz, 2H, CH$_Ar$), 6.27 (dt, $J = 15.0$, 1.4 Hz, 1H, COCH=), 4.54 (s, 2H, NCH$_2$), 4.42 (s, 2H, NCH$_2$), 3.81 (s, 3H, OCH$_3$), 3.57 (s, 3H, OCH$_3$).
3.80 (s, 3H, OCH₃), 2.22-2.12 (m, 2H, CHCH₂), 1.52-1.41 (m, 2H, CH₃CH₂), 0.90 (t, J = 7.4 Hz, 3H, CH₂CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 167.2, 159.1, 158.9, 147.6, 129.8, 129.7, 128.7, 127.9, 120.4, 114.3, 113.9, 55.4, 55.3, 49.1, 47.6, 34.6, 21.7, 13.8. HRMS (ESI+, m/Z): calcd. for C₂₂H₂₈NO₃ [M+H]+: 354.2064, found: 354.2066.

(E)-N-Methyl-N-phenylbut-2-enamide (1f)

The product 1f was synthesized following Method 3 and obtained after column chromatography (SiO₂, pentane:Et₂O = 2:1) as a colorless oil in 24% of yield. ¹H NMR (CDCl₃, 400 MHz): δ 7.46-7.37 (m, 2H, CHAr), 7.37-7.28 (m, 1H, CHAr), 7.21-7.14 (m, 2H, CHAr), 6.90 (dq, J = 15.1, 6.9 Hz, 1H, CH₃CH=), 5.73 (d, J = 15.1 Hz, 1H, COCH=), 3.30 (s, 3H, NC₃H), 1.70 (dd, J = 6.9, 1.5 Hz, 3H, CHC₃H₃).

(E)-N-Methyl-N-tosylbut-2-enamide (1g)

The product 1g was synthesized following Method 4 and obtained as a colorless oil in 97% of yield. ¹H NMR (CDCl₃, 400 MHz): δ 7.74 (d, J = 8.0 Hz, 2H, CHAr), 7.33 (d, J = 8.0 Hz, 2H, CHAr), 6.96 (dq, J = 15.0, 6.8 Hz, 1H, CH₃CH=), 6.79 (dq, J = 15.0, 1.5 Hz, 1H, COCH=), 3.27 (s, 3H, NCH₃), 2.43 (s, 3H, PhCH₃), 1.90 (dd, J = 6.8, 1.5 Hz, 3H, CHCH₃).

(E)-N-Methyl-N-methoxybut-2-enamide (1h)

The product 1h was synthesized following Method 3 and obtained after column chromatography (SiO₂, pentane:Et₂O = 2:1) as a colorless oil in 70% of yield. (Note: In this case N-methoxy-methylamine hydrochloride (8 mmol) and dry triethylamine (10 mmol) were used.) ¹H NMR (CDCl₃, 400 MHz): δ 6.98 (dq, J = 15.4, 6.9 Hz, 1H, CH₃CH=), 6.42 (dq, J = 15.4, 1.7 Hz, 1H, COCH=), 3.70 (s, 3H, OCH₃), 3.23 (s, 3H, NCH₃), 1.91 (dd, J = 6.9, 1.7 Hz, 3H, CHCH₃).

(E)-1-(4-Morpholinyl)-2-buten-1-one (1i)

The product 1i was synthesized following Method 3 and obtained after column chromatography (SiO₂, Et₂O) as a colorless oil in 92% of yield. ¹H NMR (CDCl₃, 400 MHz): δ
6.82 (dq, J = 15.0, 6.9 Hz, 1H, CH₃CH=), 6.16 (dq, J = 15.0, 1.7 Hz, 1H, COCH=), 3.61-3.50 (m, 8H, CH₂), 1.81 (dd, J = 6.9, 1.7 Hz, 3H, CHCH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 165.6, 142.1, 121.0, 66.8, 46.1, 42.2, 18.2. HRMS (ESI+, m/Z): calcd. for C₈H₁₄NO [M+H]+: 156.1019, found: 156.1019.

5,6-Dihydro-1-methyl-2(1H)-pyridinone (1j)²³

![Structure 1j]

The product 1j was synthesized following Method 5 and obtained as a colorless oil in 58% of total yield. ¹H NMR (CDCl₃, 400 MHz): δ 6.48 (dt, J = 9.7, 4.2 Hz, 1H, CH₂C=), 5.86 (dt, J = 9.7, 1.9 Hz, 1H, COC=), 3.36 (t, J = 7.2 Hz, 2H, NC₃H₂), 2.93 (s, 3H, NC₆H₃), 2.38-2.31 (m, 2H, CH₂CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 166.9, 147.1, 133.5, 133.2, 120.4, 117.4, 116.8, 49.2, 48.5, 34.7, 21.7, 13.8. HRMS (ESI+, m/Z): calcd. for C₁₂H₂₀NO [M+H]+: 194.1539, found: 194.1540.

(E)-N,N-Diallyl-hex-2-enamide (1k)

![Structure 1k]

The product 1k was synthesized following Method 1 and obtained as a colorless oil in 63% of yield. ¹H NMR (CDCl₃, 400 MHz): δ 6.93 (dt, J = 15.1, 7.0 Hz, 1H, CH=CH), 6.14 (dt, J = 15.1, 1.5 Hz, 1H, CH=CH), 5.84-5.74 (m, 2H, CH₂CH₂), 5.22-5.11 (m, 4H, CH₂CH₂), 4.02 (d, J = 5.3 Hz, 2H, CH₂CH₂), 3.92 (d, J = 4.6 Hz, 2H, CH₂CH₂), 2.21-2.13 (m, 2H, CH₂CH₂), 1.54-1.42 (m, CH₂CH₃), 0.92 (t, J = 7.3 Hz, 3H, CH₂CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 166.9, 147.1, 133.5, 133.2, 120.4, 117.4, 116.8, 49.2, 48.5, 34.7, 21.7, 13.8. HRMS (ESI+, m/Z): calcd. for C₁₂H₂₀NO [M+H]+: 194.1539, found: 194.1540.

(E)-N,N-Dimethyl-3-cyclohexyl-prop-2-enamide (1l)⁵⁰

![Structure 1l]

The product 1l was synthesized following Method 6 and obtained as a colorless liquid after column chromatography (SiO₂, Et₂O) in 14% yield. ¹H NMR (CDCl₃, 400 MHz): δ 6.82 (dd, J = 15.2, 7.0 Hz, 1H, CH=CH), 6.17 (dd, J = 15.2, 1.2 Hz, 1H, CH=CH), 3.06 (s, 3H, NCH₃), 2.99 (s, 3H, NCH₃), 2.16-2.08 (m, 1H, CH), 1.76-1.64 (m, 5H, CH₂), 1.33-1.09 (m, 5H, CH₂). HRMS (ESI+, m/Z): calcd. for C₁₁H₂₀NO [M+H]+: 182.1539, found: 182.1537.

(E)-N,N-Dimethyl-3-phenyl-prop-2-enamide (1m)⁵¹

![Structure 1m]
The product 1m was synthesized following Method 1 and obtained as a white powder in 82% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.67 (d, \(J = 15.4\) Hz, 1H, CH=CH), 7.54-7.52 (m, 2H, CHAr), 7.39-7.32 (m, 3H, CHAr), 6.89 (d, \(J = 15.4\) Hz, 1H, CH=CH), 3.17 (s, 3H, NCH\(_3\)), 3.07 (s, 3H, NCH\(_3\)).

\((E)-N,N\)-Diallyl-3-phenyl-prop-2-enamide (1n)

The product 1n was synthesized following Method 1 and obtained as a colorless oil in 90% of yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.72 (d, \(J = 15.4\) Hz, 1H, CH=CH), 7.50-7.48 (m, 2H, CHAr), 7.37-7.30 (m, 3H, CHAr), 6.78 (d, \(J = 15.4\) Hz, 1H, CH=CH), 5.89-5.78 (m, 2H, 2CH=CH\(_2\)), 5.25-5.15 (m, 4H, 2CH=CH\(_2\)), 4.09 (d, \(J = 5.8\) Hz, 2H, CH\(_2 CH\)), 4.02 (d, \(J = 4.1\) Hz, 2H, CH\(_2 CH\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 166.7, 143.0, 135.4, 133.3, 133.3, 129.6, 128.8, 127.9, 117.7, 117.5, 116.9, 49.3, 48.8. HRMS (ESI+, m/Z): calcd. for C\(_{15}\)H\(_{18}\)NO [M+H]\(^+\): 228.1384, found: 228.1383.

\((E)-N,N\)-Dimethyl-3-(4-(trifluoromethyl)phenyl)-prop-2-enamide (1o)

The product 1o was synthesized following Method 1 and obtained as a white solid in 87% of yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.67 (d, \(J = 15.4\) Hz, 1H, CH=CH), 6.96 (d, \(J = 15.5\) Hz, 1H, CH=CH), 7.62 (s, 4H, CHAr), 3.19 (s, 3H, NCH\(_3\)), 3.09 (s, 3H, NCH\(_3\)).

\((E)-N,N\)-Diallyl-3-(4-(trifluoromethyl)phenyl)-prop-2-enamide (1p)

The product 1p was synthesized following Method 1 and obtained as a colorless oil in 69% of yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.73 (d, \(J = 15.4\) Hz, 1H, CH=CH), 7.61 (d, \(J = 8.6\) Hz, 2H, CHAr), 7.59 (d, \(J = 8.6\) Hz, 2H, CHAr), 6.84 (d, \(J = 15.4\) Hz, 1H, CH=CH), 5.91-5.78 (m, 2H, 2CH=CH\(_2\)), 5.29-5.17 (m, 4H, 2CH=CH\(_2\)), 4.11 (d, \(J = 6.1\) Hz, 2H, CH\(_2 CH\)), 4.04 (d, \(J = 4.7\) Hz, 2H, CH\(_2 CH\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 166.2, 141.3, 138.9 (q, \(J = 1.3\) Hz), 133.2, 131.3 (q, \(J = 32.7\) Hz), 128.1, 125.9 (q, \(J = 3.8\) Hz), 124.0 (q, \(J = 272.3\) Hz), 120.3, 117.8, 117.1, 49.4, 49.0. HRMS (ESI+, m/Z): calcd. for C\(_{16}\)H\(_{17}\)F\(_3\)NO [M+H]\(^+\): 296.1257, found: 296.1258.
(E)-N,N-Dimethyl-3-(4-methoxyphenyl)-prop-2-enamide (1q)

The product 1q was synthesized following Method 1 and obtained as a white solid in 79% of yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.63 (d, $J = 15.4$ Hz, 1H, CH=CH), 7.48 (d, $J = 8.7$ Hz, 2H, CHAr), 6.89 (d, $J = 8.7$ Hz, 2H, CHAr), 6.76 (d, $J = 15.4$ Hz, 1H, CH=CH), 3.83 (s, 3H, OCH$_3$), 3.16 (s, 3H, NCH$_3$), 3.06 (s, 3H, NCH$_3$).

(1E)-N,N-Dimethyl-3-(3-bromophenyl)-prop-2-enamide (1r)

The product 1r was synthesized following Method 1 and obtained as a white solid in 79% of yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.69-7.66 (m, 1H, CHAr), 7.58 (d, $J = 15.5$ Hz, 1H, CH=CH), 7.49-7.44 (m, 1H, CHAr), 7.44-7.40 (m, 1H, CHAr), 7.27-7.22 (m, 1H, CHAr), 6.88 (d, $J = 15.5$ Hz, 1H, CH=CH), 3.18 (s, 3H, NCH$_3$), 3.08 (s, 3H, NCH$_3$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 166.3, 140.8, 137.6, 132.4, 130.4, 130.2, 126.8, 123.0, 119.0, 37.5, 36.1. HRMS (ESI+, m/z): calcd. for C$_{11}$H$_{13}$BrNO [M+H]$^+$: 254.0175, found: 254.0176.

(E)-N,N-Dimethyl-3-(thiophen-2-yl)-prop-2-enamide (1s)

The product 1s was synthesized following Method 1 and obtained as a brown solid in 77% of yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.79 (d, $J = 15.1$ Hz, 1H, CH=CH), 7.31 (d, $J = 5.1$ Hz, 1H, CH=CH), 7.21 (d, $J = 3.6$ Hz, 1H, CHAr), 7.03 (dd, $J = 5.1$, 3.6 Hz, 1H, CHAr), 6.69 (d, $J = 15.1$ Hz, 1H, CH=CH), 3.14 (s, 3H, NCH$_3$), 3.07 (s, 3H, NCH$_3$).

(1E)-N,N-Diallyl-3-(thiophen-2-yl)-prop-2-enamide (1t)

The product 1t was synthesized following Method 1 and obtained as a colorless oil in 88% of yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.83 (d, $J = 15.1$ Hz, 1H, CH=CH), 7.31 (d, $J = 5.0$ Hz, 1H, CHAr), 7.21 (d, $J = 3.5$ Hz, 1H, CHAr), 7.03 (dd, $J = 5.0$, 3.5 Hz, 1H, CHAr), 6.58 (d, $J = 15.1$ Hz, 1H, CH=CH), 5.92-5.76 (m, 2H, 2 CH=CH$_2$), 5.30-5.13 (m, 4H, 2 CH=CH$_2$), 4.09 (d, $J = 5.9$ Hz, 2H, CH$_2$CH), 4.00 (d, $J = 3.8$ Hz, 2H, CH$_2$CH). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 166.4, 140.6, 135.8, 133.4, 133.3, 130.3, 128.1, 127.3, 117.5, 117.0, 116.5, 49.4, 48.9. HRMS (ESI+, m/z): calcd. for C$_{13}$H$_{16}$NOS [M+H]$^+$: 234.0947, found: 234.0948.
**(E)-N,N-Dimethyl-3-(thiophen-3-yl)-prop-2-enamide (1u)**

![Structure of 1u]

The product 1u was synthesized following Method 1 and obtained as a brown solid in 72% of yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 7.66 (d, J = 15.4 \text{ Hz}, 1\text{H}, CH=CH), 7.45 (dd, J = 2.8, 1.2 \text{ Hz}, 1\text{H}, CHAr), 7.32 (dd, J = 5.1, 2.8 \text{ Hz}, 1\text{H}, CHAr), 7.30 (dd, J = 5.1, 1.2 \text{ Hz}, 1\text{H}, CHAr), 6.72 (d, J = 15.4 \text{ Hz}, 1\text{H}, CH=CH), 3.13 (s, 3\text{H}, NH\(_3\)), 3.08 (s, 3\text{H}, NH\(_3\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 166.9, 138.4, 136.1, 126.9, 126.7, 125.2, 117.1, 37.4, 36.1.\) HRMS (ESI+, m/Z): calcd. for C\(_{9}\)H\(_{12}\)NOS [M+H]\(^+\): 182.0634, found: 182.0633.

**(E)-N,N-Dimethyl-3-(3-piridinyl)-prop-2-enamide (1v)**

![Structure of 1v]

The product 1v was synthesized following Method 1 and obtained after column (SiO\(_2\), EtOAc) as a white solid in 69% of yield. (Note: In this case the reaction was quenched with saturated Na\(_2\)CO\(_3\) solution and the aqueous layer was extracted with DCM. The organic layer was dried (MgSO\(_4\)), filtered and concentrated under reduced pressure.) \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 8.70 (d, J = 1.9 \text{ Hz}, 1\text{H}, CHAr), 8.51 (dd, J = 4.7, 1.4 \text{ Hz}, 1\text{H}, CHAr), 7.80-7.75 (m, 1\text{H}, CHAr), 7.59 (d, J = 15.5, 1.2 \text{ Hz}, 1\text{H}, PyCH), 7.25 (dd, J = 7.9, 4.7 \text{ Hz}, 1\text{H}, CHAr), 6.92 (d, J = 15.5 \text{ Hz}, 1\text{H}, COCH), 3.13 (s, 3\text{H}, NCH\(_3\)), 3.02 (s, 3\text{H}, NCH\(_3\)).\)

**(E)-N,N-Dimethyl-6-bromo-hex-2-enamide (1w)**

![Structure of 1w]

The product 1w was synthesized following Method 6 and obtained as a colorless oil. (Note: In this case after purification by column chromatography (SiO\(_2\), EtOAc) a mixture of 90% title amide and 10% chloro-substituted amide was obtained. The mixture (1.5 mmol) was dissolved in CH\(_2\)Br\(_2\) (10 mL) and added to a stirred solution of tetraethylammonium bromide (3.15 g, 15 mmol) in CH\(_2\)Br\(_2\) (20 mL). The flask was fitted with a condenser and heated at 80 °C under nitrogen for 16 h. The reaction mixture was condensed under reduced pressure and Et\(_2\)O was added. The mixture was filtered and the filtrate was condensed under reduced pressure. The residue was purified by column chromatography on silica gel (SiO\(_2\), EtOAc) to afford the title amide (21% yield) as a colorless oil.) \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 6.81 (dt, J = 15.0, 7.2 \text{ Hz}, 1\text{H}, CH_2CH=), 6.32 (dt, J = 15.0, 1.4 \text{ Hz}, 1\text{H}, COCH=), 3.42 (t, J = 6.5 \text{ Hz}, 2\text{H}, BrCH\(_2\)), 3.08 (s, 3\text{H}, NCH\(_3\)), 3.00 (s, 3\text{H}, NCH\(_3\)), 2.43-2.35 (m, 2\text{H}, CH\(_2\)CH=), 2.07-1.97 (m, BrCH\(_2\)CH\(_2\)). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 166.5, 143.5, 121.7, 37.3, 35.7, 32.9, 31.0, 30.6.\) HRMS (ESI+, m/Z): calcd. for C\(_{8}\)H\(_{15}\)BrNO [M+H]\(^+\): 220.0332, found: 220.0314.
(E)-N,N-Dimethyl-6-hydroxy-hex-2-enamide (1x)

![Chemical structure of 1x]

The product 1x was synthesized following Method 6 and obtained after column chromatography (SiO₂, Et₂O:MeOH = 20:1) as a colorless oil 15% of yield. ¹H NMR (CDCl₃, 400 MHz): δ 6.87 (dt, J = 15.1, 7.0 Hz, 1H, CH₂CH=), 6.28 (dt, J = 15.1, 1.5 Hz, 1H, COCH=), 3.67 (t, J = 6.4 Hz, 2H, OCH₂), 3.07 (s, 3H, NCH₃), 2.99 (s, 3H, NCH₃), 2.36-2.26 (m, 2H, CH₂CH=), 1.79-1.68 (m, 2H, OCH₂CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 167.0, 145.8, 120.4, 61.5, 37.4, 35.7, 31.2, 28.8. HRMS (ESI+, m/Z): calcd. for C₈H₁₆NO₂ [M+H]⁺: 158.1176, found: 158.1176.

(F)-5,5,5-trifluoropent-2-enoic acid (1y)

![Chemical structure of 1y]

Allyl trifluoromethane (437 mg, 3.97 mmol) was condensed at 0 °C in a pressure proof flask and dissolved in toluene (2.5 mL). Then, Hoveyda-Grubbs II catalyst (50 mg, 0.079 mmol) and acrylic acid (545 μL, 4.94 mmol) were added, pressure tube was carefully closed and warmed up to 80 °C while stirring overnight. Then, flask was cooled down to room temperature and carefully opened, and solvent was evaporated in vacuo. The crude mixture was purified by column chromatography on silica gel (SiO₂, pentane:Et₂O = 10:1) to afford the acid (257 mg, 42% yield) as a yellowish oil. ¹H NMR (CDCl₃, 400 MHz): δ 6.94 (dt, J = 15.6, 7.2 Hz, 1H, CH=CHCH₂), 6.07 (d, J = 15.8 Hz, 1H, CH=CHCH₂), 3.17-2.90 (m, 2H, CH₂). ¹⁹F NMR (CDCl₃, 377 MHz): δ −65.4 (t, J = 10.3 Hz). ¹³C NMR (CDCl₃, 101 MHz): δ 170.7, 137.9 (q, J = 3.6 Hz), 127.0, 125.1 (q, J = 276.9 Hz), 36.9 (q, J = 30.8 Hz). HRMS (ESI+, m/Z): calcd. for C₅H₄F₃O₂ [M-H]⁻: 153.0169, found: 153.0171.

(F)-N,N-Bis(4-methoxybenzyl)hex-2-enamide (1z)

![Chemical structure of 1z]

Amide 1z was synthesized from product 1y following Method 1 and obtained after column chromatography (SiO₂, pentane:Et₂O = 2:1) as a pale yellow oil in 16% of yield. ¹H NMR (CDCl₃, 400 MHz): δ 7.19 (d, J = 8.3 Hz, 2H, CHAr), 7.07 (d, J = 8.4 Hz, 2H, CHAr), 6.91-6.84 (m, 5H, CHAr, CH₂CH=), 6.50 (dt, J = 15.2 Hz, 1H, COCH=), 4.55 (s, 2H, NCH₂), 4.42 (s, 2H, NCH₂), 3.82 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 3.02-2.92 (m, 1H, CH₂). ¹⁹F NMR (CDCl₃, 377 MHz): δ −65.5 (t, J = 10.5 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 165.8, 159.4, 159.2, 133.3 (q, J = 3.5 Hz), 130.0, 129.2, 128.2, 127.9, 127.2, 125.4 (q, J = 276.8 Hz), 114.5, 114.1, 55.44, 55.39, 49.3, 47.9, 37.1 (q, J = 30.4 Hz). HRMS (ESI+, m/Z): calcd. for C₂₁H₂₃F₃NO₃ [M+H]⁺: 394.1625, found: 394.1620.
2.4.5 Cu-catalyzed ACA of Grignards to α,β-unsaturated carboxamides

2.4.5.1 General procedures

In a flame-dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr·SMe$_2$ and ligand ($R,S_e$)-L1 were dissolved in DCM (final concentration of carboxamide substrate is 0.1M) and stirred under nitrogen atmosphere for 20 min. The substrate was added at once. After stirring for 5 min. at RT the reaction mixture was cooled down (see the details per substrate), followed by addition of LA. After 20 min., RMgBr was added by hand in about 1 min. After stirring for 18 h, the reaction was quenched with MeOH followed by addition of saturated aqueous NH$_4$Cl solution and warming up to RT. The reaction mixture was extracted with DCM (10 mL × 3). Combined organic phases were dried over MgSO$_4$, filtered and solvents were evaporated on a rotary evaporator. The crude was purified by flash chromatography on silica gel. (Note 1: The procedures for ACA differ in LA, the reaction temperature and mode of addition. The details are given per product. The reactions were carried out either using 0.1 or 0.2 mmol of an carboxamide substrate. Note 2: DCM was found to be the most optimal solvent while presence of even traces of THF is detrimental for the reaction conversion and enantioselectivity. On the other hand Cu salts other than CuBr can be used as well as long as the halide in the Grignard reagent used is a bromide (RMgBr). Note 3: Grignard reagents must be used either in Et$_2$O or MTBE. THF even in a small quantities must be avoided. Copper catalyzed conjugate addition of THF solution of i-PrMgBr for instance led to racemic product while Et$_2$O solution afforded product wih 76% ee.)

2.4.5.2 Procedure for the preparative (10 g) scale Cu-catalyzed ACA using 5 mol% of chiral catalyst and the recovery of the chiral catalyst L1/Cu(I)

The reaction on a preparative scale (Table 3, entry 3) was carried out for the synthesis of the product 3h using the general procedure described above. The reaction was carried out using 1a (10 g, 71 mmol), CuBr·SMe$_2$ (727.9 mg, 3.54 mmol, 5 mol%), ligand L1 (2721.2 mg, 4.25 mmol, 6 mol%), TMSOTf (25.6 mL, 141.6 mmol), MeMgBr (141.6 mmol, 3.0 M in Et$_2$O), 708 mL of DCM at 0 °C, for a total reaction time of 2h. Product 3h was obtained as a colorless oil [93% yield, 96% ee] after column chromatography (SiO$_2$, pentane:Et$_2$O = 1:1). The chiral catalyst was recovered in this reaction in the form of a Cu-complex L1/Cu(I). The reaction mixture was loaded on a column with silica. Using a pentane:Et$_2$O ratio of 1:1 the L1/Cu(I) eluted first, followed by CA product 3h. Catalyst L1/Cu(I) was obtained as a yellow-orange solid in 80% of yield and reused for another ACA reaction (Table 3, entry 4) with similar performance.

2.4.5.3 General procedure for the synthesis of racemic products

Racemic products were synthesized in a flame-dried Schlenk tube equipped with septum and magnetic stirring bar by mixing the corresponding carboxamide substrate (0.1 M in DCM) with 2 equiv. of corresponding Grignard reagents and 1.1 equiv. of TMSOTf at −10 °C for 2 h. The quenching and isolation procedure is the same as described above.
2.4.5.4 Specific experimental details and product characterization

(R)-N,N-Dimethyl-3-ethyl-hexanamide (2a)

![Chemical structure of (R)-N,N-Dimethyl-3-ethyl-hexanamide (2a)]

The reaction was performed with 0.2 mmol 1a, CuBr·SMe₂ (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF₃·Et₂O (50 μL, 0.4 mmol), EtMgBr (0.4 mmol, 3.0 M in Et₂O), 2.0 mL of DCM at -78 °C. Product 2a was obtained as a colorless oil after column chromatography (SiO₂, pentane:EtO = 1:1) [73% yield, 97% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 3.00 (s, 3H, NC₃H₃), 2.93 (s, 3H, NC₃H₃), 2.21 (dd, J = 15.1, 7.1 Hz, 1H, CH₂CO), 1.91-1.81 (m, 1H, CHCH₂), 1.36-1.21 (m, 5H, CH₂CH₃, CH₂CH₂CH₃), 1.24-1.18 (m, 1H, CH₂CH₂), 0.87 (d, J = 7.0 Hz, 3H, CH₃), 0.85 (t, J = 7.5 Hz, 3H, CH₂CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 173.1, 37.8, 37.6, 36.1, 35.9, 35.5, 26.4, 19.9, 14.5, 11.0. HRMS (ESI+, m/Z): calcd. for C₁₀H₂₀NO [M+H]⁺: 172.1696, found: 172.1696. HPLC: Chiracel-OBH, n-heptane/i-PrOH 95:5, 0.5 mL/min, 40 °C, detection at 210 nm. Retention time (min): 10.4 (minor) and 11.5 (major).

(S)-N,N-Dimethyl-3-methyl-pentanamide (2b)

![Chemical structure of (S)-N,N-Dimethyl-3-methyl-pentanamide (2b)]

The reaction was performed with 0.2 mmol 1b, CuBr·SMe₂ (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF₃·Et₂O (50 μL, 0.4 mmol), EtMgBr (0.4 mmol, 3.0 M in Et₂O), 2.0 mL of DCM at -78 °C. Product 2b was obtained as a colorless oil after column chromatography (SiO₂, EtO) [79% yield, 94% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 3.00 (s, 3H, NCH₃), 2.94 (s, 3H, NCH₃), 2.30 (dd, J = 14.7, 5.9 Hz, 1H, CHHCO), 2.11 (dd, J = 14.7, 8.1 Hz, 1H, CHHCO), 1.98-1.86 (m, 1H, CHCH₂), 1.44-1.34 (m, 1H, CHHCH₃), 1.24-1.14 (m, 1H, CHHCH₃), 0.92 (t, J = 7.3 Hz, 3H, CH₂CH₂), 0.89 (t, J = 7.3 Hz, 3H, CH₂CH₂). HPLC: Chiracel-OBH, n-heptane/i-PrOH 90:10, 0.5 mL/min, 40 °C, detection at 209 nm. Retention time (min): 10.7 (major) and 13.1 (minor).

(S)-N,N-Diallyl-3-methyl-pentanamide (2c)

![Chemical structure of (S)-N,N-Diallyl-3-methyl-pentanamide (2c)]

The reaction was performed with 0.2 mmol 1c, CuBr·SMe₂ (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF₃·Et₂O (50 μL, 0.4 mmol), EtMgBr (0.4 mmol, 3.0 M in Et₂O), 2.0 mL of DCM at -78 °C. Product 2c was obtained as a colorless oil after column chromatography (SiO₂, pentane:EtO = 5:1) [52% yield, 98% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 5.80-5.70 (m, 2H, CH=CH₂), 5.20-5.08 (m, 4H, CH=CH₂), 4.05-3.91 (m, 2H,
NCH$_2$CH=CH$_2$), 3.90-3.84 (m, 2H, NCH$_2$CH=CH$_2$), 2.28 (dd, $J = 14.9, 5.9$ Hz, 1H, CHHCO), 2.10 (dd, $J = 14.9, 8.0$ Hz, 1H, CHHCO), 2.02-1.90 (m, 1H, CHCH$_2$), 1.43-1.33 (m, 1H, CH$_3$CHH), 1.22-1.13 (m, 1H, CH$_3$CHH), 0.91 (d, $J = 6.6$ Hz, 3H, CH$_3$CH), 0.88 (t, $J = 7.5$ Hz, 3H, CH$_3$CH$_2$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 172.8, 133.6, 133.2, 117.1, 116.6, 49.3, 47.9, 40.1, 32.0, 29.7, 19.6, 11.6. HRMS (ESI+, m/Z): calcd. for C$_{12}$H$_{22}$NO [M+H]$^+$: 196.1696, found: 196.1693.

HPLC: Chiracel-ODH, n-heptane/i-PrOH 99.1: 0.5 mL/min, 40 °C, detection at 211 nm. Retention time (min): 14.9 (minor) and 16.0 (major).

(S)-N,N-Dibenzyl-3-methyl-pentanamide (2d)

The reaction was performed with 0.2 mmol 1d, CuBr-SMe$_2$ (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF$_3$·Et$_2$O (50 $\mu$L, 0.4 mmol), EtMgBr (0.4 mmol, 3.0 M in Et$_2$O), 2.0 mL of DCM at −78 °C. Product 2d was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 5:1) [78% yield, 97% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.39-7.27 (m, 6H, CHAr), 7.23 (d, $J = 7.4$ Hz, 2H, CHAr), 7.16 (d, $J = 7.4$ Hz, 2H, CHAr), 4.65 (d, $J = 14.7$ Hz, 1H, NCH$_2$), 4.58 (d, $J = 14.7$ Hz, 1H, NCH$_2$), 4.46 (s, 2H, NCH$_2$), 2.42 (dd, $J = 15.0, 5.8$ Hz, 1H, CHHCO), 2.24 (dd, $J = 15.0, 8.0$ Hz, 1H, CHHCO), 2.11-2.02 (m, 1H, CH), 1.45-1.40 (m, 1H, CH$_3$CHH), 1.24-1.19 (m, 1H, CH$_3$CHH), 0.97 (d, $J = 6.6$ Hz, 3H, CH$_3$CH), 0.90 (t, $J = 7.4$ Hz, 3H, CH$_3$CH$_2$). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 173.3, 137.8, 136.8, 129.0, 128.7, 128.4, 127.7, 127.4, 126.5, 50.0, 48.1, 40.3, 32.2, 19.6, 11.6. HRMS (ESI+, m/Z): calcd. for C$_{20}$H$_{26}$NO [M+H]$^+$: 296.2009, found: 296.2008.

HPLC: Chiracel-ODH, n-heptane/i-PrOH 99.5:0.5, 0.8 mL/min, 40 °C, detection at 218 nm. Retention time (min): 37.4 (minor) and 38.5 (major).

(R)-N,N-Bis(4-methoxybenzyl)-3-ethyl-hexanamide (2e)

The reaction was performed with 0.1 mmol 1e, CuBr-SMe$_2$ (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), BF$_3$·Et$_2$O (38 $\mu$L, 0.3 mmol), EtMgBr (0.2 mmol, 3.0 M in Et$_2$O), 1.0 mL of DCM at −78 °C. Product 2e was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 4:1) [72% yield, 98% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.15 (d, $J = 8.6$ Hz, 2H, CHAr), 7.07 (d, $J = 8.6$ Hz, 2H, CHAr), 6.84 (d, $J = 8.6$ Hz, 2H, CHAr), 6.84 (d, $J = 8.6$ Hz, 2H, CHAr), 4.51 (s, 2H, NCH$_2$), 4.37 (s, 2H, NCH$_2$), 3.81 (s, 3H, OCH$_3$), 3.79 (s, 3H, OCH$_3$), 2.33 (dd, $J = 15.4, 7.1$ Hz, 1H, CHHCO), 2.31 (dd, $J = 15.4, 6.7$ Hz, 1H, CHHCO), 2.00-1.97 (m, 1H, CH), 1.40-1.28 (m, 6H, CH$_3$CH$_2$, CH$_3$CH$_2$CH$_2$), 0.90-0.84 (m, 6H, CH$_3$CH$_2$). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 173.3, 159.1, 159.0, 129.9, 129.8, 128.7, 127.8,
114.3, 114.0, 55.4, 55.4, 49.2, 47.2, 37.8, 36.3, 35.8, 26.4, 19.9, 14.5, 11.0. HRMS (ESI+, m/Z): calcd. for C_{24}H_{34}NO_{3} [M+H]^+: 384.2533, found: 384.2537. HPLC: Chiracel-ADH, n-heptane/i-PrOH 95:5, 0.5 mL/min, 40 °C, detection at 227 nm. Retention time (min): 32.5 (major) and 35.5 (minor).

(S)-N-Methyl-N-phenyl-3-methyl-pentanamide (2f)

The reaction was performed with 0.2 mmol 1f, CuBr-SMe_{2} (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF_{3}-Et_{2}O (50 μL, 0.4 mmol), EtMgBr (0.4 mmol, 3.0 M in Et_{2}O), 2.0 mL of DCM at −78 °C. Product 2f was obtained as a colorless oil after column chromatography (SiO_{2}, pentane:Et_{2}O = 3:1) [66% yield, 77% ee]. {\textsuperscript{1}}H NMR (CDCl_{3}, 400 MHz): δ 7.45-7.37 (m, 2H, CHAr), 7.36-7.28 (m, 1H, CHAr), 7.19-7.12 (m, 2H, CHAr), 3.25 (s, 3H, NCH_{3}), 2.08-2.06 (m, 1H, CHHCO), 1.91-1.83 (m, 2H, CHHCO, CH), 1.24-1.20 (m, 1H, CH_{3}CH), 1.06-1.03 (m, 1H, CH_{3}CHH), 0.81 (d, J = 6.0 Hz, 3H, CH_{3}CH), 0.75 (t, J = 7.4 Hz, 3H, CH_{3}CH_{2}). {\textsuperscript{13}}C NMR (CDCl_{3}, 100 MHz): δ 172.9, 144.5, 129.8, 127.7, 127.6, 41.0, 37.5, 32.3, 29.5, 19.5, 11.5. HRMS (ESI+, m/Z): calcd. for C_{13}H_{20}NO [M+H]^+: 206.1539, found: 206.1540. HPLC: Chiracel-OZH, n-heptane/i-PrOH 95:5, 0.5 mL/min, 40 °C, detection at 245 nm. Retention time (min): 18.0 (major) and 19.9 (minor).

(S)-N-Methyl-N-tosyl-3-methyl-pentanamide (2g)

The reaction was performed with 0.1 mmol 1g, CuBr-SMe_{2} (2.06 mg, 0.01 mmol, 10 mol%), ligand L1 (7.68 mg, 0.012 mmol, 12 mol%), BF_{3}-Et_{2}O (25 μL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et_{2}O), 1.0 mL of DCM at −78 °C. Product 2g was obtained as a colorless oil after column chromatography (SiO_{2}, pentane:Et_{2}O = 10:1) [83% yield, 86% ee]. (Note: When the reaction was carried out in the absence of Lewis acid the product 2g was obtained in 60% yield and 36% ee.) {\textsuperscript{1}}H NMR (CDCl_{3}, 400 MHz): δ 7.76 (d, J = 8.3 Hz, 2H, CHAr), 7.33 (d, J = 8.0 Hz, 2H, CHAr), 3.29 (s, 3H, NCH_{3}), 2.61 (dd, J = 16.3, 5.7 Hz, 1H, CHHCO), 2.46 (dd, J = 16.3, 7.9 Hz, 1H, CHHCO), 2.43 (s, 3H, PhCH_{3}), 1.98-1.86 (m, 1H, CH_{3}CH), 1.35-1.25 (m, 1H, CH_{3}CHH), 1.19-1.08 (m, 1H, CH_{3}CHH), 0.83 (d, J = 6.6 Hz, 3H, CH_{3}CH), 0.82 (t, J = 7.4 Hz, 3H, CH_{3}CH_{2}). {\textsuperscript{13}}C NMR (CDCl_{3}, 100 MHz): δ 173.1, 144.9, 136.6, 129.9, 127.7, 127.5, 43.4, 33.2, 31.6, 29.4, 21.8, 19.3, 11.4. HRMS (ESI+, m/Z): calcd. for C_{14}H_{23}N_{3}OS [M+H]^+: 284.1315, found: 284.1315. HPLC: Chiracel-OZH, n-heptane/i-PrOH 99.2:0.8, 0.5 mL/min, 40 °C, detection at 235 nm. Retention time (min): 94.7 (major) and 107.0 (minor).
(S)-N-Methyl-3-methyl-pentanamide (2h)

The reaction was performed with 0.2 mmol 1h, CuBr-SMe2 (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF3·Et2O (50 μL, 0.4 mmol), EtMgBr (0.4 mmol, 3.0 M in Et2O), 2.0 mL of DCM at −78 °C. Product 2h was obtained as a colorless oil after column chromatography (SiO2, Et2O) [65% yield, 95% ee]. (Note: Only demethoxylated product 2h, most likely promoted by the Grignard reagent, was obtained. Decreasing the amount of Grignard reagent to 0.2 mmol led to decrease in the substrate conversion (which was also demthoxylated) and once again 2h was the major product.)

1H NMR (CDCl3, 400 MHz): δ 5.61 (br s, 1H, NH), 2.79 (d, J = 4.9 Hz, 3H, NCH3), 2.20-2.13 (m, 1H, CHHCO), 1.94-1.82 (m, 1H, CHHCO, CH), 1.40-1.30 (m, 1H, CH3CHH), 0.90 (d, J = 6.2 Hz, 3H, CH3CH), 0.87 (t, J = 7.4 Hz, 3H, CH3CH2). 13C NMR (CDCl3, 100 MHz): δ 173.6, 44.3, 32.4, 29.6, 26.3, 19.3, 11.4. HRMS (ESI+, m/Z): calcd. for C7H16NO [M+H]+: 130.1226, found: 130.1227. HPLC: Chiracel-ASH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 207 nm. Retention time (min): 29.8 (major) and 35.3 (minor).

(R)-4-Ethyl-1-methylpiperidin-2-one (2j)

The reaction was performed with 0.2 mmol 1j, CuBr-SMe2 (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), EtMgBr (0.4 mmol, 3.0 M in Et2O) in 2.0 mL of
DCM at −50 °C. Product 2j was obtained as a pale yellow oil after column chromatography (SiO₂, Et₂O) [75% yield, 93% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 3.30-3.27 (m, 2H, CH₂N), 2.93 (s, 3H, NCH₃), 2.54-2.48 (m, 1H, CH), 2.00-1.88 (m, 2H, CH₂CO), 1.75-1.64 (m, 1H, CH₂CHHCH), 1.49-1.39 (m, 1H, CH₂CHHCH), 1.37-1.25 (m, 2H, CH₂CH₃), 0.91 (t, J = 7.3 Hz, 3H, CH₃CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 170.1, 49.4, 38.6, 34.9, 34.6, 28.9, 28.6, 11.2. HRMS (ESI+, m/Z): calcd. for C₁₈H₂₆NO [M+H]+: 286.1726, found: 286.1726. HPLC: Chiracel-ODH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 202 nm. Retention time (min): 43.0 (major) and 45.7 (minor).

**(R)-N,N-Diallyl-3-ethylhexanamide (2k)**

The reaction was performed with 0.2 mmol 1k, CuBr·SMe₂ (2.06 mg, 0.01 mmol, 5 mol%), ligand L₁ (7.68 mg, 0.012 mmol, 6 mol%), BF₃·Et₂O (50 μL, 0.4 mmol), EtMgBr (0.4 mmol, 3.0 M in Et₂O), 2.0 mL of DCM at −78 °C. Product 2k was obtained as a colorless oil after column chromatography (SiO₂, pentane:Et₂O = 5:1) [71% yield, 98% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 5.80-5.70 (m, 2H, CH=CH₂), 5.20-5.07 (m, 4H, CH=CH₂), 4.02-3.96 (m, 2H, NC₃H₂CH=CH₂), 3.91-3.95 (m, 2H, NC₃H₂CH=CH₂), 2.21 (dd, J = 15.2, 7.2 Hz, 1H, CHHCO), 2.20 (dd, J = 15.2, 6.6 Hz, 1H, CHHCO), 1.95-1.86 (m, 1H, CHH₂), 1.36-1.21 (m, 6H, CH₃), 0.88 (t, J = 6.8 Hz, 3H, CH₃), 0.85 (t, J = 7.4 Hz, 3H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 173.0, 133.6, 133.2, 117.1, 116.6, 49.3, 48.0, 37.5, 36.1, 35.6, 26.4, 26.0, 19.9, 14.5, 11.0. HRMS (ESI+, m/Z): calcd. for C₁₄H₂₆NO [M+H]⁺: 224.2009, found: 224.2011. HPLC: Chiracel-ADH, n-heptane/i-PrOH 99.2:0.8, 0.5 mL/min, 40 °C, detection at 220 nm. Retention time (min): 23.8 (major) and 25.5 (minor).

**(S)-N,N-Dimethyl-3-cyclohexyl-pentanamide (2l)**

The reaction was performed with 0.1 mmol 1l, CuBr·SMe₂ (1.03 mg, 0.005 mmol, 5 mol%), ligand L₁ (3.84 mg, 0.006 mmol, 6 mol%), BF₃·Et₂O (25 μL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et₂O), 1.0 mL of DCM at −78 °C. Product 2l was obtained as a colorless oil after column chromatography (SiO₂, pentane:Et₂O = 1:1) [71% yield, 93% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 3.01 (s, 3H, NC₃H₃), 2.94 (s, 3H, NCH₃), 2.30 (dd, J = 15.1, 5.7 Hz, 1H, CHHCO), 2.13 (dd, J = 15.1, 7.8 Hz, 1H, CHHCO), 1.77-1.57 (m, 6H, CH₂, CH), 1.42-0.96 (m, 8H, CH₂, CH), 0.86 (t, J = 7.4 Hz, 3H, CH₃CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 173.5, 41.8, 40.0, 37.6, 35.7, 34.7, 30.2, 29.4, 27.00, 26.96 (2C), 23.8, 12.0. HRMS (ESI+, m/Z): calcd. for C₁₃H₂₆NO [M+H]⁺: 212.2009, found: 212.2008. HPLC: Chiracel-OZH, n-heptane/i-PrOH 95:5, 0.5 mL/min, 40 °C, detection at 206 nm. Retention time (min): 20.6 (major) and 22.2 (minor).
(S)-N,N-Dimethyl-3-phenylpentanamide (2m)

![2m]

The reaction was performed with 0.1 mmol 1m, CuBr·SMe₂ (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), BF₃·Et₂O (25 μL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et₂O), 1.0 mL of DCM at −78 °C. Product 2m was obtained as a colorless oil after column chromatography (SiO₂, pentane:Et₂O = 1:2) [70% yield, 94% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 7.30-7.26 (m, 2H, CHAr), 7.21-7.17 (m, 3H, CHAr), 3.13-3.03 (m, 1H, CH₂), 2.87 (s, 3H, NC₃H₃), 2.83 (s, 3H, NC₃H₃), 2.60 (dd, J = 15.1, 6.9 Hz, 1H, CHHCO), 2.56 (dd, J = 15.1, 7.2 Hz, 1H, CHHCO), 1.86-1.73 (m, 1H, CHHCH₃), 1.69-1.55 (m, 1H, CHHCH₃), 0.79 (t, J = 7.4 Hz, 3H, CH₂CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 172.0, 144.9, 128.5, 127.8, 126.4, 44.2, 40.6, 37.5, 35.5, 28.9, 12.3. HRMS (ESI+, m/Z): calcd. for C₁₃H₂₀NO [M+H]+: 206.1539, found: 206.1540. HPLC: Chiracel-ODH, n-heptane/i-PrOH 90:10, 0.5 mL/min, 40 °C, detection at 208 nm. Retention time (min): 12.1 (major) and 13.3 (minor).

(S)-N,N-Diallyl-3-phenylpentanamide (2n)

![2n]

The reaction was performed with 0.1 mmol 1n, CuBr·SMe₂ (2.06 mg, 0.01 mmol, 10 mol%), ligand L1 (7.68 mg, 0.012 mmol, 12 mol%), BF₃·Et₂O (25 μL, 0.2 mmol), in 1.0 mL of DCM at −78 °C and slow addition of a solution of EtMgBr (0.2 mmol, 3.0 M in Et₂O) in 0.5 mL of toluene and added dropwise to the reaction mixture during 2 h using a syringe pump. Product 2n was obtained as a colorless oil after column chromatography (SiO₂, pentane:Et₂O = 5:1) [63% yield, 93% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 7.30-7.28 (m, 2H, CHAr), 7.20-7.17 (m, 3H, CHAr), 5.70-5.60 (m, 2H, CH=CH₂), 5.18-4.90 (m, 4H, CH₂=CH), 4.00 (dd, J = 15.3, 5.7, 1H, CHHCH⁻), 3.82 (dd, J = 15.3, 5.9, 1H, CHHCH⁻), 3.78-3.65 (m, 2H, CH₂CH=), 3.18-3.08 (m, 1H, CH), 2.57 (d, J = 7.2 Hz, 2H, CH₂CO), 1.82-1.72 (m, 1H, CHHCH₃), 1.65-1.54 (m, 1H, CHHCH₃), 0.79 (t, J = 7.3 Hz, 3H, CH₃CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 172.0, 144.7, 133.4, 133.0, 128.5, 127.9, 126.4, 117.0, 116.6, 49.2, 48.0, 44.2, 40.2, 29.0, 12.3. HRMS (ESI+, m/Z): calcd for C₁₇H₂₄NO [M+H]+: 258.1855, found: 258.1852. HPLC: Chiracel-ADH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 208 nm. Retention time (min): 21.9 (major) and 26.6 (minor).

(S)-N,N-Dimethyl-3-{4-(trifluoromethyl)phenyl}pentanamide (2o)

![2o]
The reaction was performed with 0.1 mmol 1o, CuBr-SMe2 (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), BF3-Et2O (25 µL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et2O), 1.0 mL of DCM at −78 °C. Product 2o was obtained as a colorless oil after column chromatography (SiO₂, Et₂O) [81% yield, 96% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 7.54 (d, J = 8.1 Hz, 2H, CHAr), 7.33 (d, J = 8.1 Hz, 2H, CHAr), 3.25-3.15 (m, 1H, CH), 2.89 (s, 3H, NCH₃), 2.88 (s, 3H, NCH₃), 2.60 (d, J = 7.0 Hz, 2H, CH₂CO), 1.87-1.74 (m, 1H, CHHCH₃), 1.69-1.55 (m, 1H, CHHCH₃), 0.79 (t, J = 7.3 Hz, 3H, CH₃CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 171.4, 149.2 (q, J = 11 Hz), 128.2, 125.4 (q, J = 3.8 Hz), 124.4 (q, J = 272.0 Hz), 43.9, 40.1, 37.4, 35.6, 29.0, 12.1. HRMS (ESI⁺, m/Z): calcd. for C₁₄H₁₉F₃NO [M+H]+: 274.1413, found: 274.1414. HPLC: Chiracel-ADH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 203 nm. Retention time (min): 21.9 (major) and 29.7 (minor).

(SP)-N,N-Diallyl-3-(4-trifluoromethyl)phenylpentanamide (2p)

The reaction was performed with 0.1 mmol 1p, CuBr-SMe₂ (2.06 mg, 0.01 mmol, 10 mol%), ligand L1 (7.68 mg, 0.012 mmol, 12 mol%), BF₃-Et₂O (25 µL, 0.2 mmol), in 1.0 mL of DCM at −78 °C and slow addition of a solution of EtMgBr (0.2 mmol, 3.0 M in Et₂O) in 0.5 mL of toluene and added dropwise to the reaction mixture during 2 h using a syringe pump. Product 2p was obtained as a colorless oil after column chromatography (SiO₂, pentane:Et₂O = 5:1) [67% yield, 90% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 7.53 (d, J = 7.8 Hz, 2H, CHAr), 7.31 (d, J = 7.8 Hz, 2H, CHAr), 5.72-5.59 (m, 2H, CH = CH₂), 5.19-4.89 (m, 4H, CH₂=CH), 3.98-3.82 (m, 2H, CH₂CH=), 3.79-3.72 (m, 2H, CH₂CH=), 3.29-3.19 (m, 1H, CH), 2.59 (dd, J = 15.6, 6.9 Hz, 1H, CHHCO), 2.59 (dd, J = 15.6, 7.4 Hz, 1H, CHHCO), 1.84-1.71 (m, 1H, CHHCH₃), 1.67-1.52 (m, 1H, CHHCH₃), 0.78 (t, J = 7.3 Hz, 3H, CH₃CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 171.4, 149.0, 133.2, 132.8, 129.0 (q, J = 30.7 Hz), 128.2, 125.4 (q, J = 3.7 Hz), 124.4 (q, J = 272.1 Hz), 117.1, 116.6, 49.2, 48.2, 43.9, 39.7, 29.0, 12.2. HRMS (ESI⁺, m/Z): calcd. for C₁₈H₁₄F₃NO [M+H]+: 326.1726, found: 326.1730. HPLC: Chiracel-ADH, n-heptane/i-PrOH 95.5: 0.5 mL/min, 40 °C, detection at 209 nm. Retention time (min): 11.7 (major) and 15.1 (minor).

(SP)-N,N-Dimethyl-3-(4-methoxyphenyl)pentanamide (2q)

The reaction was performed with 0.1 mmol 1q, CuBr-SMe₂ (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), BF₃-Et₂O (25 µL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et₂O), 1.0 mL of DCM at −78 °C. Product 2q was obtained as a colorless oil after column chromatography (SiO₂, pentane:Et₂O = 1:10) [70% yield, 97% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 7.12 (d, J = 8.6 Hz, 2H, CHAr), 6.83 (d, J = 8.6 Hz, 2H, CHAr), 3.78 (s, 3H, OCH₃), 3.08-2.98 (m, 1H, CH), 2.87 (s, 3H, NCH₃), 2.60 (d, J = 15.5, 7.1 Hz, 1H, 52
CHCO) 2.54 (dd, J = 15.5, 7.1 Hz, 1H, CHHCO), 1.83-1.71 (m, 1H, CHHCH$_3$), 1.65-1.50 (m, 1H, CHHCH$_3$), 0.78 (t, J = 7.3 Hz, 3H, CH$_3$CH$_2$). $^1$C NMR (CDCl$_3$, 100 MHz): δ 172.2, 158.1, 136.9, 128.6, 113.8, 53.5, 43.5, 40.9, 37.5, 35.6, 29.1, 12.3. HRMS (ESI+, m/z): calcd. for C$_{14}$H$_{22}$NO [M+H]$^+$: 236.1645, found: 236.1645. HPLC: Chiracel-OJH, n-heptane/i-PrOH 90:10, 0.5 mL/min, 40 °C, detection at 210 nm. Retention time (min): 14.0 (major) and 16.4 (minor).

(S)-$N,N$-Dimethyl-3-(3-bromophenyl)pentanamide (2r)

The reaction was performed with 0.1 mmol 1r, CuBr-SMe$_2$ (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), BF$_3$-Et$_2$O (25 μL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et$_2$O), 1.0 mL of DCM at −78 °C. Product 2r was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 1:2) [74% yield, 95% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.34-7.30 (m, 2H, CH$_2$Ar), 7.15-7.14 (m, 2H, CH$_2$Ar), 3.13-3.03 (m, 1H, CH), 2.88 (s, 6H, NC$_3$H$_3$), 2.55 (d, J = 7.0 Hz, 2H, CH$_2$CO), 1.83-1.69 (m, 1H, CHHCH$_3$), 1.64-1.50 (m, 1H, CHHCH$_3$), 0.78 (t, J = 7.4 Hz, 3H, CH$_3$CH$_2$). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 171.5, 147.5, 130.6, 130.0, 129.5, 126.8, 122.6, 43.9, 40.2, 37.4, 35.6, 29.0, 12.2. HRMS (ESI+, m/z): calcd. for C$_{13}$H$_{19}$BrNO [M+H]$^+$: 284.0645, found: 284.0647. HPLC: Chiracel-ODH, n-heptane/i-PrOH 97:3, 0.5 mL/min, 40 °C, detection at 210 nm. Retention time (min): 22.0 (major) and 26.0 (minor).

(S)-$N,N$-Dimethyl-3-(thiophen-2-yl)pentanamide (2s)

The reaction was performed with 0.1 mmol 1s, CuBr-SMe$_2$ (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), BF$_3$-Et$_2$O (25 μL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et$_2$O), 1.0 mL of DCM at −78 °C. Product 2s was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 1:5) [85% yield, 95% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.13 (d, J = 5.1 Hz, 1H, CH$_2$Ar), 6.91 (dd, J = 5.1, 3.4 Hz, 1H, CH$_2$Ar), 6.83 (d, J = 3.4 Hz, 1H, CH$_2$Ar), 3.49-3.42 (m, 1H, CH), 2.90 (s, 3H, NCH$_3$), 2.89 (s, 3H, NCH$_3$), 2.64 (dd, J = 15.2, 7.1, Hz, 1H, CHHCO), 2.58 (dd, J = 15.2, 6.9, Hz, 1H, CHHCO), 1.89-1.76 (m, 1H, CHHCH$_3$), 1.69-1.55 (m, 1H, CHHCH$_3$), 0.88 (t, J = 7.2 Hz, 3H, CH$_3$CH$_2$). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 171.6, 148.9, 126.7, 124.2, 123.0, 41.4, 39.6, 37.4, 35.6, 30.3, 12.2. HRMS (ESI+, m/z): calcd. for C$_{13}$H$_{18}$NOS [M+H]$^+$: 212.1104, found: 212.1104. HPLC: Chiracel-ADH, n-heptane/i-PrOH 90:10, 0.5 mL/min, 40 °C, detection at 218 nm. Retention time (min): 10.7 (major) and 11.9 (minor).
The reaction was performed with 0.1 mmol 1t, CuBr·SMe2 (2.06 mg, 0.01 mmol, 10 mol%), ligand L1 (7.68 mg, 0.012 mmol, 12 mol%), BF3·Et2O (25 μL, 0.2 mmol), in 1.0 mL of DCM at −78 °C and slow addition of a solution of EtMgBr (0.2 mmol, 3.0 M in Et2O) in 0.5 mL of toluene and added dropwise to the reaction mixture during 2 h using a syringe pump. Product 2t was obtained as a colorless oil after column chromatography (SiO2, pentane:Et2O = 5:1) [63% yield, 91% ee]. 1H NMR (CDCl3, 400 MHz): δ 7.13 (d, J = 5.0 Hz, 1H, CHAr), 6.91 (dd, J = 5.0, 3.4 Hz, 1H, CHAr), 6.83 (d, J = 3.4 Hz, 1H, CHAr), 5.74-5.63 (m, 2H, CH=CH2), 5.16 (d, J = 10.4, 1H, CH=CH), 5.10-5.04 (m, 2H, CH2=CH), 4.99 (d, J = 17.1, 1H, CH=CH), 4.04 (dd, J = 15.3, 5.5 Hz, 1H, CHHCH=), 3.84-3.69 (m, 2H, CH2CH=), 3.73 (dd, J = 17.5, 4.7 Hz, 2H, CH2CH=), 3.54-3.47 (m, 1H, CH), 2.62 (dd, J = 15.1, 7.3 Hz, 1H, CHHCO), 2.57 (dd, J = 15.1, 6.8 Hz, 1H, CHHCO), 1.83-1.75 (m, 1H, CHHCH3), 1.66-1.54 (m, 1H, CHHCH3), 0.87 (t, J = 7.3 Hz, 3H, CH3CH2). 13C NMR (CDCl3, 100 MHz): δ 171.5, 148.7, 133.4, 132.9, 126.6, 124.4, 123.0, 117.1, 116.6, 49.2, 48.2, 41.1, 39.6, 30.3, 12.2. HRMS (ESI+, m/Z): calcd. for C15H22NOS [M+H]+: 264.1417, found: 264.1419. HPLC: Chiracel-ADH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 232 nm. Retention time (min): 21.6 (major) and 26.2 (minor).

The reaction was performed with 0.1 mmol 1u, CuBr·SMe2 (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), BF3·Et2O (25 μL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et2O), 1.0 mL of DCM at −78 °C. Product 2u was obtained as a colorless oil after column chromatography (SiO2, pentane:Et2O = 1:5) [63% yield, 96% ee]. 1H NMR (CDCl3, 400 MHz): δ 7.24 (dd, J = 5.0, 3.0 Hz, 1H, CHAr), 6.98 (ddd, J = 3.0, 1.3, 0.5 Hz, 1H, CHAr), 6.98 (dd, J = 5.0, 1.3 Hz, 1H, CHAr) 3.29-3.20 (m, 1H, CH), 2.89 (s, 3H, NCH3), 2.84 (s, 3H, NCH3), 2.56 (dd, J = 14.9, 7.0, Hz, 1H, CHHCO), 2.53 (dd, J = 14.9, 7.0, Hz, 1H, CHHCO), 1.83-1.70 (m, 1H, CHHCH3), 1.67-1.54 (m, 1H, CHHCH3), 0.82 (t, J = 7.4 Hz, 3H, CH3CH2). 13C NMR (CDCl3, 100 MHz): δ 172.1, 145.7, 126.9, 125.4, 120.3, 40.3, 39.5, 37.4, 35.6, 29.0, 12.2. HRMS (ESI+, m/Z): calcd. for C11H18NOS [M+H]+: 212.1104, found: 212.1104. HPLC: Chiracel-OBH, n-heptane/i-PrOH 90:10, 0.5 mL/min, 40 °C, detection at 209 nm. Retention time (min): 13.9 (major) and 17.1 (minor).
**{(S)-N,N-Dimethyl-3-(3-pyridinyl)pentanamide (2v)}**

The reaction was performed with 0.1 mmol 1v, CuBr·SMe2 (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), BF3·Et2O (25 μL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et2O), 1.0 mL of DCM at ~78 °C. Product 2v was obtained as a colorless oil after column chromatography (SiO2 previously treated with NEt3 (10%), Et2O:MeOH = 30:1) [74% yield, 95% ee]. (Note: In this case the reaction was quenched with 2 M NaOH solution.)

1H NMR (CDCl3, 400 MHz): δ 8.44 (s, 1H, CHAr), 8.41 (d, J = 4.8 Hz, 1H, CHAr), 7.54-7.49 (m, 1H, CHAr), 3.18-3.04 (m, 1H, CH3H), 2.87 (s, 3H, NH3), 2.84 (s, 3H, NH3), 2.59 (dd, J = 15.4, 6.7 Hz, 1H, CHHCO), 2.57 (dd, J = 15.4, 7.4 Hz, 1H, CHHCO), 1.85-1.72 (m, 1H, CH2CH3), 1.67-1.53 (m, 1H, CH2CH3), 0.77 (t, J = 7.4 Hz, 3H, CH3CH2). 13C NMR (CDCl3, 100 MHz): δ 171.2, 149.5, 147.9, 140.2, 135.5, 123.5, 41.7, 40.0, 37.4, 35.6, 28.9, 12.1. HRMS (ESI+, m/Z): calcd. for C12H19N2O [M+H]+: 207.1492, found: 207.1487. HPLC: Chiracel-ODH, n-heptane/i-PrOH 80:20, 0.5 mL/min, 40 °C, detection at 208 nm. Retention time (min): 13.7 (major) and 15.2 (minor).

**{(R)-N,N-Dimethyl-6-bromo-3-ethyl-hexanamide (2w)}**

The reaction was performed with 0.1 mmol 1w, CuBr·SMe2 (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), BF3·Et2O (25 μL, 0.2 mmol), EtMgBr (0.2 mmol, 3.0 M in Et2O), 1.0 mL of DCM at ~78 °C. Product 2w was obtained as a colorless oil after column chromatography (SiO2, pentane:Et2O = 1:1) [76% yield, 97% ee]. 1H NMR (CDCl3, 400 MHz): δ 3.40 (dt, J = 12.0, 6.8 Hz, 1H, CHBr), 3.38 (dt, J = 12.0, 6.8 Hz, 1H, CHBr), 3.00 (s, 3H, NH3), 2.94 (s, 3H, NH3), 2.28 (dd, J = 15.3, 6.5 Hz, 1H, CHHCO), 2.18 (dd, J = 15.3, 7.1 Hz, 1H, CHHCO), 1.97-1.82 (m, 3H, CH2CH3, CH2CH2Br), 1.46-1.32 (m, 4H, CH2CH3, CH2CH2CH2Br), 0.88 (t, J = 7.4 Hz, 3H, CH3CH2). 13C NMR (CDCl3, 100 MHz): δ 172.6, 149.5, 147.9, 140.2, 135.5, 123.5, 41.7, 40.0, 37.4, 35.6, 28.9, 12.1. HRMS (ESI+, m/Z): calcd. for C10H19BrNO [M+H]+: 250.0801, found: 250.0805. HPLC: Chiracel-ODH, n-heptane/i-PrOH 95:5, 0.5 mL/min, 40 °C, detection at 207 nm. Retention time (min): 15.1 (major) and 16.7 (minor).

**{(R)-N,N-Dimethyl-6-hydroxy-3-ethyl-hexanamide (2x)}**

The reaction was performed with 0.1 mmol 1x, CuBr·SMe2 (1.03 mg, 0.005 mmol, 5 mol%), ligand L1 (3.84 mg, 0.006 mmol, 6 mol%), TMSOTf (54 μL, 0.3 mmol), EtMgBr (0.3 mmol, 3.0 M in Et2O), 1.0 mL of DCM at ~50 °C. Product 2x was obtained as a colorless oil after...
column chromatography (SiO$_2$, Et$_2$O:MeOH = 30:1) [71% yield, 93% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.69-3.58 (m, 2H, CH$_2$OH), 3.00 (s, 3H, NCH$_3$), 2.93 (s, 3H, NCH$_3$), 2.30 (dd, $J$ = 15.5, 5.4 Hz, 1H, CHHCO), 2.15 (dd, $J$ = 15.5, 8.4 Hz, 1H, CHHCO), 1.93-1.86 (m, 1H, CH), 1.65-1.35 (m, 2H, CH$_2$CH$_2$OH), 1.46-1.35 (m, 2H, CH$_2$CH$_2$CH$_2$OH), 1.34-0.87 (t, $J$ = 7.4 Hz, 3H, CH$_3$CH$_2$). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 173.2, 62.5, 37.7, 37.5, 35.6, 35.1, 29.7, 29.4, 26.6. HRMS (ESI+, m/Z): calcd. for C$_{10}$H$_{22}$NO [M+H]$^+$: 188.1645, found: 188.1643. HPLC: Chiracel-OJH, n-heptane/i-PrOH 95:5, 0.5 mL/min, 40 °C, detection at 209 nm. Retention time (min): 16.4 (minor) and 17.3 (major).

**(R)-N,N-Dimethyl-3-cyclopentyl-hexanamide (3a)**

The reaction was performed with 0.2 mmol 1a, CuBr·SMe$_2$ (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), TMSOTf (72 $\mu$L, 0.4 mmol), c-PentMgBr (0.4 mmol, 2.0 M in Et$_2$O), 2.0 mL of DCM at −50 °C. Product 3a was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 2:1) [78% yield, 87% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.01 (s, 3H, NCH$_3$), 2.93 (s, 3H, NCH$_3$), 2.28 (dd, $J$ = 15.2, 5.6 Hz, 1H, CHHCO), 2.22 (dd, $J$ = 15.2, 7.5 Hz, 1H, CHHCO), 1.96-1.44 (m, 8H, CH$_2$, C$_2$H$_2$), 1.38-0.87 (t, $J$ = 6.9 Hz, 3H, CH$_3$CH$_2$). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 173.3, 43.9, 39.1, 37.6, 36.4, 35.6, 35.1, 30.1, 30.0, 25.6, 25.5, 19.8, 14.7. HRMS (ESI+, m/Z): calcd. for C$_{13}$H$_{26}$NO [M+H]$^+$: 212.2009, found: 212.2008. HPLC: Chiracel-OZH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 205 nm. Retention time (min): 36.2 (minor) and 38.8 (major).

**(S)-N,N-Dimethyl-5-methyl-3-propyl-hexanamide (3b)**

The reaction was performed with 0.2 mmol 1a, CuBr·SMe$_2$ (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), TMSOTf (72 $\mu$L, 0.4 mmol), i-BuMgBr (0.4 mmol, 2.0 M in Et$_2$O), 2.0 mL of DCM at −50 °C. Product 3b was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 2:1) [84% yield, 95% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.99 (s, 3H, NCH$_3$), 2.93 (s, 3H, NCH$_3$), 2.22 (dd, $J$ = 15.1, 7.3 Hz, 1H, CHHCO), 2.17 (dd, $J$ = 15.1, 6.4 Hz, 1H, CHHCO), 2.03-1.93 (m, 1H, CH$_3$CH$_2$CH$_2$CH$_2$), 1.67-1.54 (m, 1H, CH$_3$CH$_2$), 1.34-1.21 (m, 4H, CH$_3$CH$_2$, CH$_3$CH$_2$CH$_2$), 1.19-1.04 (m, 2H, CH$_3$CHCH$_2$), 0.90-0.84 (m, 9H, CH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 173.1, 44.1, 38.6, 37.6, 36.8, 35.6, 32.5, 25.5, 23.1, 22.9, 19.7, 14.6. HRMS (ESI+, m/Z): calcd. for C$_{12}$H$_{26}$NO [M+H]$^+$: 200.2009, found: 200.2007. HPLC: Chiracel-ADH, n-heptane/i-PrOH 95:5, 0.5 mL/min, 40 °C, detection at 219 nm. Retention time (min): 45.5 (major) and 49.2 (minor).
(S)-N,N-Dimethyl-6-methy-3-propyl-heptanamide (3c)

The reaction was performed with 0.2 mmol 1a, CuBr·SMe2 (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF3·Et2O (50 μL, 0.4 mmol), i-PentMgBr (0.4 mmol, 2.0 M in Et2O), 2.0 mL of DCM at −78 °C. Product 3c was obtained as a colorless oil after column chromatography (SiO2, pentane:Et2O = 2:1) [77% yield, 97% ee]. 1H NMR (CDCl3, 400 MHz): δ 2.99 (s, 3H, NC3H3), 2.93 (s, 3H, NC3H3), 2.21 (d, J = 6.9 Hz, 2H, CH2CO), 1.94-1.84 (m, 1H, CH3CH2CH), 1.52-1.41 (m, 1H, CH3C3H), 1.34-1.19 (m, 6H, CH2), 1.17-1.11 (m, 2H, CH3CHCH2), 0.87 (t, J = 6.7 Hz, 3H, CH3CH2CH2), 0.85 (d, J = 6.6 Hz, 6H, CH3CH). 13C NMR (CDCl3, 100 MHz): δ 173.1, 38.2, 37.6, 36.4, 35.9, 35.6, 34.9, 31.8, 28.4, 22.8, 22.7, 19.9, 14.5. HRMS (ESI+, m/Z): calcd. for C13H28NO [M+H]+: 214.2165, found: 214.2165. HPLC: Chiracel-ODH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 206 nm. Retention time (min): 12.7 (major) and 13.5 (minor).

(S)-N,N-Dimethyl-3-phenethylhexanamide (3d)

The reaction was performed with 0.2 mmol 1a, CuBr·SMe2 (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF3·Et2O (50 μL, 0.4 mmol), phenylethylMgBr (0.4 mmol, 2.6 M in Et2O), 2.0 mL of DCM at −78 °C. Product 3d was obtained as an orange oil after column chromatography (SiO2, pentane:Et2O = 1:1) [73% yield, 97% ee]. 1H NMR (CDCl3, 400 MHz): δ 7.28-7.25 (m, 2H, CHAr), 7.19-7.14 (m, 3H, CHAr), 2.96 (s, 3H, NC3H3), 2.94 (s, 3H, NCH3), 2.67-2.55 (m, 2H, CH2Ph), 2.30 (dd, J = 15.9, 7.0 Hz, 1H, CHHCO), 2.28 (dd, J = 15.9, 6.8 Hz, 1H, CHHCO), 2.07-1.97 (m, 1H, CH), 1.66-1.60 (m, 2H, CH2CH3), 1.38-1.28 (m, 4H, CH2CH2CH3 and CH2CH2Ph), 0.90 (t, J = 6.9 Hz, 3H, CH3CH2). 13C NMR (CDCl3, 100 MHz): δ 172.8, 142.9, 128.5, 128.4, 125.8, 38.2, 37.6, 36.4, 36.0, 35.6, 34.6, 33.3, 19.9, 14.6. HRMS (ESI+, m/Z): calcd. for C16H26NO [M+H]+: 248.2009, found: 248.2010. HPLC: Chiracel-OJH, n-heptane/i-PrOH 95:5, 0.5 mL/min, 40 °C, detection at 210 nm. Retention time (min): 12.8 (major) and 13.8 (minor).

(S)-N,N-Dimethyl-3-propyl-oct-7-enamide (3e)

The reaction was performed with 0.2 mmol 1a, CuBr·SMe2 (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF3·Et2O (50 μL, 0.4 mmol), pent-4-en-1-ylMgBr
(0.4 mmol, 1.7 M in Et$_2$O), 2.0 mL of DCM at $-78 \, ^\circ$C. Product 3e was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 1:1) [80% yield, 97% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 5.86-5.73 (m, 1H, CH=CH$_2$), 5.02-4.94 (m, 1H, CH=CHH), 4.94-4.89 (m, CH=CHH), 2.99 (s, 3H, NCH$_3$), 2.93 (s, 3H, NCH$_3$), 2.23 (dd, $J = 15.4$, 6.9 Hz, 1H, CHHCO), 2.19 (dd, $J = 15.4$, 6.9 Hz, 1H, CHHCO), 2.05-1.99 (m, 2H, CH$_2$CH=CH$_2$), 1.97-1.90 (m, 1H, CHCH$_2$CO). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 173.0, 139.1, 114.4, 38.2, 37.6, 36.4, 35.6, 34.6, 34.2, 33.6, 26.1, 19.9, 14.5. HRMS (ESI+, m/Z): calcd. for C$_{13}$H$_{26}$NO [M+H]$^+$: 228.2322, found: 228.2322. HPLC: Chiracel-ODH, n-heptane/i-PrOH 99:7:0.3, 0.5 mL/min, 40 °C, detection at 215 nm. Retention time (min): 40.8 (major) and 45.9 (minor).

(S)-N,N-Dimethyl-3-propyl-nonanamide (3f)

\[
\begin{align*}
\text{(3f)} & \\
\text{The reaction was performed with 0.2 mmol 1a, CuBr-SMe$_2$ (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF$_3$-Et$_2$O (50 $\mu$L, 0.4 mmol), n-HexMgBr (0.4 mmol, 2.0 M in Et$_2$O), 2.0 mL of DCM at $-78 \, ^\circ$C. Product 3f was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 1:1) [82% yield, 97% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.99 (s, 3H, NCH$_3$), 2.93 (s, 3H, NCH$_3$), 2.21 (d, $J = 6.9$ Hz, 2H, CH$_2$CO), 1.92-1.89 (m, 1H, CH), 1.32-1.17 (m, 14H, CH), 0.87 (t, $J = 6.6$ Hz, 3H, CH$_3$), 0.86 (t, $J = 6.9$ Hz, 3H, CH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 173.1, 38.2, 37.6, 36.5, 35.6, 34.8, 34.1, 32.0, 29.8, 26.7, 22.8, 19.9, 14.5, 14.2. HRMS (ESI+, m/Z): calcd. for C$_{14}$H$_{30}$NO [M+H]$^+$: 228.2322, found: 228.2321. HPLC: Chiracel-ODH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 206 nm. Retention time (min): 12.7 (major) and 13.5 (minor).}
\end{align*}
\]

(S)-N,N-Dimethyl-7-chloro-3-propyl-heptanamide (3g)

\[
\begin{align*}
\text{(3g)} & \\
\text{The reaction was performed with 0.2 mmol 1a, CuBr-SMe$_2$ (2.06 mg, 0.01 mmol, 5 mol%), ligand L1 (7.68 mg, 0.012 mmol, 6 mol%), BF$_3$-Et$_2$O (50 $\mu$L, 0.4 mmol), (4-chlorobutyl)MgBr (0.4 mmol, 1.3 M in Et$_2$O), 2.0 mL of DCM at $-78 \, ^\circ$C. Product 3g was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 1:1) [41% yield, 98% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.54 (t, $J = 6.6$ Hz, 2H, CH$_2$Cl), 3.01 (s, 3H, NCH$_3$), 2.95 (s, 3H, NCH$_3$), 2.26 (dd, $J = 15.2$, 6.7 Hz, 1H, CHHCO), 2.20 (dd, $J = 15.2$, 7.0 Hz, 1H, CHHCO), 1.98-1.94 (m, 1H, CH), 1.80-1.73 (m, 2H, CH$_2$CH$_2$Cl), 1.48-1.40 (m, 2H, CH$_2$CH$_2$CH$_2$Cl), 1.35-1.25 (m, 6H, CH$_2$), 0.89 (t, $J = 6.7$ Hz, 3H, CH$_3$CH$_2$). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 172.9, 45.2, 38.0, 37.6, 36.4, 35.6, 34.5, 33.3, 32.9, 24.0, 19.9, 14.5. HRMS (ESI+, m/Z): calcd. for C$_{12}$H$_{25}$ClNO [M+H]$^+$: 234.1619, found: 234.1622. HPLC: Chiracel-ODH, n-heptane/i-PrOH 99:5:0.5, 0.5 mL/min, 40 °C, detection at 216 nm. Retention time (min): 70.4 (major) and 77.1 (minor).}
\end{align*}
\]
(R)-N,N-Dimethyl-3-methyl-hexanamide (3h)

The reaction was performed with 0.2 mmol 1a, CuBr·SMe₂ (2.06 mg, 0.01 mmol, 5 mol%), ligand L₁ (7.68 mg, 0.012 mmol, 6 mol%), TMSOTf (72 μL, 0.4 mmol), MeMgBr (0.4 mmol, 3.0 M in Et₂O), 2.0 mL of DCM at −50 °C. Product 3h was obtained as a colorless oil after column chromatography (SiO₂, pentane:Et₂O = 1:1) [93% yield, 99% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 3.00 (s, 3H, NC₃H₃), 2.95 (s, 3H, NC₃H₃), 2.29 (dd, J = 14.6, 5.8 Hz, 1H, CH₂HCO), 2.12 (dd, J = 14.6, 8.1 Hz, 1H, CH₂CO), 2.05-1.97 (m, 1H, CH₂CH₃), 1.43-1.24 (m, 3H, CH₂CH₃, CHHCH₂CH₃), 1.19-1.10 (m, 1H, CH₂CH₂CH₃), 0.93 (d, J = 6.6 Hz, 3H, CH₃), 0.89 (t, J = 7.0 Hz, 3H, CH₂CH₂CH₃).

¹³C NMR (CDCl₃, 100 MHz): δ 172.9, 40.8, 39.5, 37.6, 35.5, 30.2, 20.3, 20.0, 14.4. HRMS (ESI+, m/Z): calcd. for C₉H₂₀NO [M+H]⁺: 158.1539, found: 158.1538. HPLC: Chiracel-OBH, n-heptane/i-PrOH 90:10, 0.5 mL/min, 40 °C, detection at 206 nm. Retention time (min): 9.1 (minor) and 10.2 (major).

(S)-N,N-Dimethyl-3-(4-(trifluoromethyl)phenyl)butanamide (3i)

The reaction was performed with 0.1 mmol 1o, CuBr·SMe₂ (1.03 mg, 0.005 mmol, 5 mol%), ligand L₁ (3.84 mg, 0.006 mmol, 6 mol%), BF₃·Et₂O (25 μL, 0.2 mmol), MeMgBr (0.2 mmol, 3.0 M in Et₂O), 1.0 mL of DCM at −78 °C. Product 3i was obtained as a colorless oil after column chromatography (SiO₂, Et₂O) [54% yield, 99% ee]. ¹H NMR (CDCl₃, 400 MHz): δ 7.54 (d, J = 8.1 Hz, 2H, CHAr), 7.36 (d, J = 8.1 Hz, 2H, CHAr), 3.52-3.40 (m, 1H, CH₂), 2.91 (s, 6H, NCH₃), 2.62 (dd, J = 15.3, 6.7 Hz, 1H, CH₂HCO), 2.54 (dd, J = 15.3, 7.3 Hz, 1H, CH₂HCO), 1.33 (d, J = 6.9 Hz, 3H, CH₃CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 171.3, 150.9, 128.7 (q, J = 32.3 Hz), 127.4, 125.5 (q, J = 3.8 Hz), 124.4 (q, J = 272.4 Hz), 41.5, 37.4, 36.4, 35.7, 21.8. HRMS (ESI+, m/Z): calcd. for C₁₃H₁₇F₃NO [M+H]⁺: 260.1257, found: 260.1261. HPLC: Chiracel-ADH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 208 nm. Retention time (min): 23.0 (major) and 28.3 (minor).

(S)-5,5,5-trifluoro-N,N-bis(4-methoxybenzyl)-3-methylpentanamide (3j)

The reaction was performed with 0.1 mmol 1z, CuBr·SMe₂ (1.03 mg, 0.005 mmol, 5 mol%), ligand L₁ (3.84 mg, 0.006 mmol, 6 mol%), BF₃·Et₂O (37 μL, 0.3 mmol), MeMgBr (0.3 mmol, 3.0 M in Et₂O), 1.0 mL of DCM at −78 °C. Product 3j was obtained as a colorless oil after
column chromatography (SiO$_2$, Et$_2$O) [62% yield, 99% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.14 (d, $J = 8.4$ Hz, 2H, CHAr), 7.04 (d, $J = 8.5$ Hz, 2H, CHAr), 6.90 (d, $J = 8.5$ Hz, 2H, CHAr), 6.85 (d, $J = 8.4$ Hz, 2H, CHAr), 4.52 (s, 2H, NC$_2$H$_5$), 4.35 (s, 2H, NCH$_2$), 3.82 (s, 3H, OCH$_3$), 3.80 (s, 3H, OCH$_3$), 2.58-2.24 (m, 4H, C$_2$H$_2$), 2.08-1.94 (m, 1H, CH), 1.10 (d, $J = 6.6$ Hz, 3H, CH$_3$). $^{19}$F NMR (CDCl$_3$, 377 MHz): $\delta$ -63.0 (t, $J = 11.3$ Hz).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 171.5, 159.3, 159.1, 129.8, 129.6, 128.3, 127.7, 127.2 (q, $J = 277.8$ Hz), 114.5, 114.1, 55.5, 55.4, 49.2, 47.5, 39.8, 29.8, 25.4 (q, $J = 2.4$ Hz), 20.3. HRMS (ESI+, m/Z): calcd. for C$_{22}$H$_{27}$F$_3$NO$_3$ [M+H]$^+$: 410.1938, found: 410.1938. HPLC: Chiracel-ODH, n-heptane/i-PrOH 99:1, 0.5 mL/min, 40 °C, detection at 226 nm. Retention time (min): 67.4 (major) and 75.6 (minor).

$^{N,N}$-Dimethyl-3-methyl-butanamide (3k)$^{27}$

\[
\text{R} \quad \text{N} \quad \text{O} \\
3k
\]

The reaction was performed with 0.2 mmol 1b, CuBr-SMe$_2$ (2.06 mg, 0.01 mmol, 5 mol%), TMSOTf (72 μL, 0.4 mmol), MeMgBr (0.4 mmol, 3.0 M in Et$_2$O), 2.0 mL of DCM at −10 °C. Product 3k was obtained as a colorless oil after column chromatography (SiO$_2$, pentane:Et$_2$O = 1:1) [63% yield]. $^1$H NMR (CD$_2$Cl$_2$, 400 MHz): $\delta$ 2.93 (s, 3H, NC$_3$H$_2$), 2.84 (s, 3H, NC$_3$H$_2$), 2.12 (d, $J = 7.0$ Hz, 2H, CH$_2$CO), 2.00 (nonuplet, $J = 6.7$ Hz, 1H, CH$_2$CH), 0.87 (d, $J = 6.6$ Hz, 6H, (CH$_3$)$_2$CH).

2.4.6 Applications of the catalytic method

2.4.6.1 Deprotection of protecting group at the Nitrogen

(R)-3-Ethyl-hexanamide (4)

\[
\text{R} \quad \text{NH}_2 \\
4
\]

The product 4 was prepared by a literature procedure.$^{44}$ 2e (0.2 mmol) was dissolved in trifluoroacetic acid (4.0 mL) and heated to reflux for 17 h at 90 °C. The product solution was concentrated under reduced pressure. After the addition of DCM (4 mL), the organic layer was washed with saturated aqueous NaHCO$_3$ (4 mL). The aqueous layer was extracted with DCM (10 mL × 3) and the combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (SiO$_2$, Et$_2$O) to afford product 4 as a white powder [92% yield, 98% ee]. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 5.37 (br s, 2H, NH$_2$), 2.14 (dd, $J = 14.5$, 7.5 Hz, 1H, CHCO), 2.13 (dd, $J = 14.5$, 6.9 Hz, 1H, CH/CO), 1.85-1.80 (m, 1H, CH), 1.43-1.25 (m, 6H, CH$_2$), 0.90 (t, $J = 6.6$ Hz, 3H, CH$_3$), 0.88 (t, $J = 7.4$ Hz, 3H, CH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 176.0, 40.8, 36.5, 35.6, 26.2, 19.8, 14.5, 10.8. HRMS (ESI+, m/Z): calcd. for C$_8$H$_{18}$NO [M+H]$^+$: 144.1383, found: 144.1383. HPLC: Chiracel-ASH, n-heptane/i-PrOH 90:10, 0.5 mL/min, 40 °C, detection at 204 nm. Retention time (min): 13.9 (major) and 16.0 (minor).
2.4.6.2 Transformation of amide into $\beta$- and $\gamma$-branched amines

(R)-3-Ethyl-hexan-1-amine (5)

A solution of 4 (50.1 mg, 0.35 mmol, 97% ee) in anhydrous THF (3.5 mL) cooled at 0 °C was added under nitrogen a solution of LiAlH$_4$ (1.0 M in Et$_2$O, 0.7 mL, 0.7 mmol). The resulting mixture was stirred at ambient temperature (1 h) and then heated to 60 °C for 18 h. The reaction was quenched with NaOH (2.0 M, 2.0 mL) and extracted with DCM (10 mL × 3). The organic layer was then dried (MgSO$_4$), filtered and concentrated under reduced pressure. The residue was redissolved in Et$_2$O (5 mL), filtered and concentrated under reduced pressure to afford product 5 as a light yellow oil [85% yield, 97% ee].

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.68 (t, 2H, J = 7.4 Hz, CH$_2$NH$_2$), 1.43-1.13 (m, 11H, CH, CH$_2$, NH$_2$), 0.88 (t, $J = 6.7$ Hz, 3H, CH$_3$), 0.84 (t, $J = 7.4$ Hz, 3H, CH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 40.1, 37.8, 36.5, 35.7, 26.0, 19.8, 14.6, 10.8. HRMS (ESI+, m/Z): calcd. for C$_8$H$_{20}$N [M+H]$^+$: 130.1590, found: 130.1590. The ee of this compound was determined from the corresponding N-benzoyl derivate. HPLC: Chiracel-ODH, n-heptane/i-PrOH 98:2, 0.5 mL/min, 40 °C, detection at 223 nm. Retention time (min): 95.0 (major) and 101.7 (minor).

(R)-2-Ethylpentan-1-amine hydrochloride (6)

The compound was prepared following the literature procedure. $^5$ m-Chloroperbenzoic acid (72% purity, 290 mg, 1.2 mmol) was dried under vacuum for 15 min at room temperature prior to use. To a stirred solution of m-CPBA in DCM (1 mL) and water (99 $\mu$l) was added a 48% aqueous solution of tetrafluoroboric acid (155 $\mu$l, 1.2 mmol), a 0.89 M DCM solution of iodobenzene (55 $\mu$l, 0.05 mmol) and then 4 (143.1 mg, 1.0 mmol, 97% ee) at 25 °C under nitrogen and the mixture was stirred for 48 h. A 10% aqueous HCl solution (2 mL) was added and the reaction mixture was extracted with DCM four times. Combined organic phase was extracted with 10% aqueous HCl solution two times. Combined aqueous phase was concentrated under reduced pressure. Product 6 was obtained as a white solid in 91% yield and 97% ee. $^1$H NMR (D$_2$O, 400 MHz): $\delta$ 2.84 (d, $J = 6.1$ Hz, 2H, CH$_2$NH$_2$), 1.61-1.51 (m, 1H, CH), 1.32-1.15 (m, 6H, CH$_2$), 0.80-0.76 (m, 6H, CH$_3$). $^{13}$C NMR (D$_2$O, 100 MHz): $\delta$ 45.0, 39.3, 34.5, 25.3, 21.3, 15.9, 12.1. HRMS (ESI+, m/Z): calcd. for C$_7$H$_{18}$N [M+H]$^+$: 116.1434, found: 116.1432. The ee of this compound was determined from the corresponding N-benzoyl derivate. HPLC: Chiracel-OBH, n-heptane/i-PrOH 99:1, 0.5 mL/min, 40 °C, detection at 222 nm. Retention time (min): 52.5 (minor) and 55.4 (major).
2.4.6.3 Catalytic ACA followed by intramolecular trapping

(1R,2R)-2-Ethyl-N,N-dimethylcyclopentane-1-carboxamide (7)

In a flame-dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr·SMe₂ (2.06 mg, 0.01 mmol, 5 mol%), and ligand L1 (7.68 mg, 0.012 mmol, 6 mol%) were dissolved in DCM (2 mL) and stirred under nitrogen atmosphere for 20 min. Amide 1v (0.2 mmol) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to −78 °C and EtMgBr (0.4 mmol, 3.0 M in Et₂O) was added. Immediately after TMSOTf (72 μL, 0.4 mmol) was added. After stirring at −78 °C for 18 h, the reaction was warmed up to RT and stirred for 8 h. The resulting reaction mixture was quenched with saturated aqueous NH₄Cl solution and extracted with DCM (10 mL × 3). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated on rotary evaporator. Product 7 was obtained as a colorless oil after column chromatography (SiO₂, pentane:Et₂O = 1:1) [66% yield, 92% ee]. Relative configuration was determined by NOE experiments (Figure 2). ¹H NMR (CDCl₃, 400 MHz): δ 3.05 (s, 3H, NCH₃), 2.96 (s, 3H, NCH₃) 2.48-2.58 (m, 1H, CHCO), 2.29-2.19 (m, 1H, CHCHCO), 1.99-1.84 (m, 2H, CH₂), 1.78-1.61 (m, 3H, CH₂), 1.52-1.41 (m, 1H, CH₂), 1.29-1.13 (m, 2H, CH₂), 0.88 (t, J = 7.4 Hz, 3H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 176.3, 49.6, 45.8, 37.4, 35.8, 31.9, 30.7, 28.0, 24.7, 12.9. HRMS (ESI+, m/Z): calcd. for C₁₀H₂₀NO [M+H]+:170.1545, found:170.1538. HPLC: Chiracel-OZH, n-heptane/i-PrOH 95:5, 0.5 mL/min, 40 °C, detection at 202 nm. Retention time (min): 16.0 (major) and 18.7 (minor).
2.5 References


