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

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Chapter 2

Copper Catalysed Conjugate Addition of Grignard Reagents to Alkenyl Aromatic Heterocycles

*In this chapter, the asymmetric copper catalysed addition of Grignard reagents to poorly reactive alkenyl aromatic heterocycles is described. Use of boron trifluoride etherate (BF$_3$·OEt$_2$) was essential to unlock the reactivity of the substrates. The protocol can be applied to several aromatic heterocycles using a wide range of Grignard reagents affording the desired products in excellent yields and enantioselectivities.*

2.1 Introduction

As already mentioned in the introduction of this thesis, heterocycles are key structures in pharmaceuticals and bioactive compound.[1] The majority of all known active pharmaceutical ingredients (APIs) contains one or more aromatic heterocyclic moieties in their structure, with *N*-containing aromatic heterocycles being the most common.[2] Moreover, many bioactive compounds often exist as chiral molecules, and the two different enantiomers exhibit markedly different activities in the living organisms. These data make clear the reason why achieving high stereocontrol in the production of APIs is a requirement of fundamental importance. Developing synthetic strategies that allow the total control on the stereochemical outcome of a chemical transformation has been always one of the main challenges for organic chemistry. Among the different class of chemical transformations, direct asymmetric C-C bond formation reactions are most sought after.[3] Conjugate addition (CA) of nucleophilic moieties to electron deficient alkenes (Michael acceptors) is an efficient and well-known method for the formation of new C-C bonds.[4,5] In this context the enantioselective addition of carbon nucleophiles to conjugated alkenyl aromatic heterocycles is an intriguing approach to access chiral aromatic heterocycle derivatives in enantiopure form (Scheme 1).
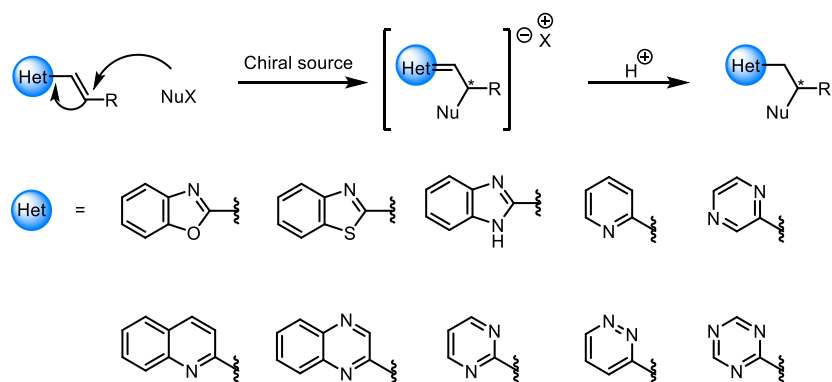
Scheme 1: Enantioselective nucleophilic addition to conjugated alkenyl aromatic heterocycles.

While addition of carbon nucleophiles (both stabilised and non-stabilised) to vinyl heteroaromatic compounds is well known,[6] there is only a handful of reports for β-substituted analogues, especially with organometallic nucleophiles. A first attempt to use conjugated alkenyl heteroaromatic compounds as Michael acceptors appeared in literature in 1998.[7] In that work, a catalytic system based on a chiral Nickel complex was employed to promote the conjugate addition of aryl magnesium bromide to 4-substituted alkenyl pyridines. Despite the desired products were obtained with moderate to good yields, the process exhibited poor enantioselectivity with only 15% of enantiomeric excess as best result (Scheme 2).
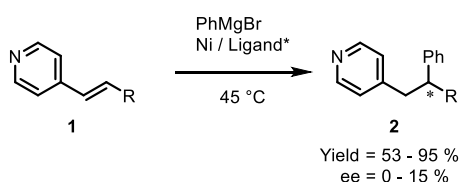
Scheme 2: Ni catalysed conjugate addition of Grignard reagent to alkenyl pyridines.

Research in this field has been silent until 2010 when Lam and co-workers developed highly enantioselective addition of organoboronic acids to alkenyl substituted heteroaromatic compounds using Rh chiral complexes as catalyst (Scheme 3).[8]
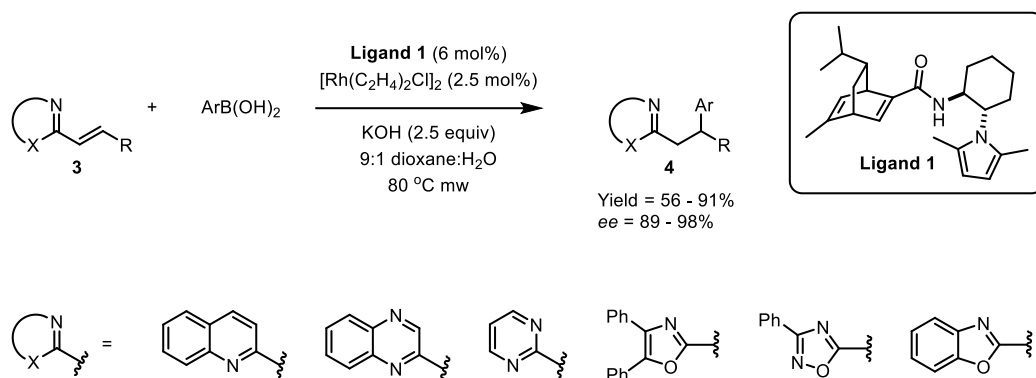
**Scheme 3:** Rh-catalysed asymmetric conjugate addition of arylboronic acid to alkenyl heteroaromatic compounds.

Using this catalytic system it was possible to obtain the desired addition products in good to excellent yields and with enantiomeric excesses (*ee's*) above 90% in most of the cases. Remarkably, several heteroarmatic compounds were compatible with this protocol, but unfortunately introduction of alkyl chains was not reported. Few years later, Lautens and co-workers developed a domino synthetic strategy for the synthesis of aza-dihydrodibenzoxepines with moderate yields and excellent *ee*'s (Scheme 4).[9] This strategy exploited the reactivity of Rh catalyst to promote the formal conjugate addition of aryl-boronic ester to electron poor alkenyl pyridines, and Pd catalyst for the *C-O* coupling for the ring closure.
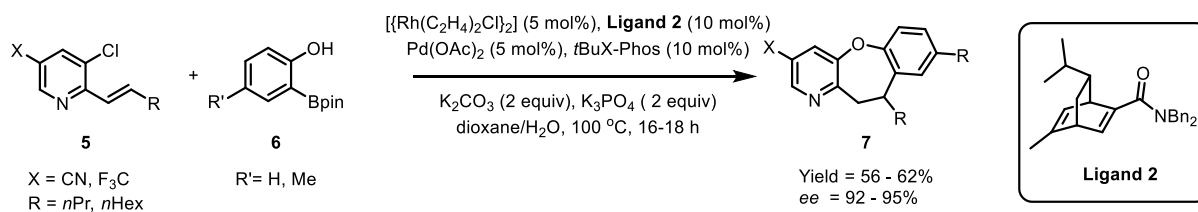

Scheme 4: Domino sequence for the synthesis of aza-dihydrodibenzoxepines catalysed by Rh and Pd.

While the asymmetric addition of different non stabilised-carbon nucleophiles, both aliphatic and aromatic, to common Michael acceptors is a well-established transformation,[5] the conjugate addition to β-substituted alkenyl aromatic heterocycles is in an early stage. The scarce amount of reports on this topic is due to the poor reactivity of β-substituted alkenyl aromatic heterocycles. Compared with the typical electron withdrawing group used in Michael-type reaction to activate the conjugated double bond, such as carbonyl, nitriles, sulfonyl and nitro group, the aromatic heterocycle has a poor tendency to activate adjacent olefinic moieties. Moreover seems reasonable to assume that the reactivity of these uncommon Michael acceptors is strongly dependant on the ease with which the aromaticity of the heterocycles can be altered. To tackle the poor reactivity of these substrates we decide to exploit the high reactivity of Grignard reagent, while copper was choice as metal catalyst due to its well-known ability to direct preferentially the addition of non-stabilised carbon nucleophiles to the β-position of α,β-unsaturated carbonyl compounds as demonstrated by the plethora of reports appeared in literature after the seminal work of Kharash and Tawney.[10]

2.2 Results and Discussion

To test our hypothesis, 2-styrylbenzoxazole **10a** was chosen as model compound. This molecule can be easily obtained in gram scale by simple condensation of benzaldehyde **9** with 2-methylbenzoxazole **8** upon treatment with *t*BuOK in THF/*t*BuOH (Scheme 5).[7]
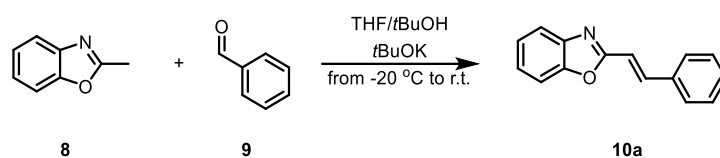
Scheme 5: Synthesis of 2-styrylbenzoxazole **10a**.

First, substrate **10a** was subjected to different reaction conditions (Table 1) in which the effects of every components of the reaction were separately explored. As expected, no conversion towards product **14a** was detected when Grignard reagents were added to **10a** at low temperature in presence of catalytic amount of CuBr·SMe$_2$ (Table 1, entry 1). Addition of chiral diphosphine ligand **L1-Cu** complex to the reaction mixture, did not improve the outcome (Table 1, entry 2). These results highlighted again the marked low reactivity of alkenyl heteroaromatics and the necessity of a stronger activation of the substrate. We aimed to enhance the reactivity of aromatic heterocycles by combining our catalytic system, namely chiral diphosphine copper complexes and Grignard reagents, with strong Lewis acid (LA) additives commonly used to enhance the reactivity of various electrophiles.[11] Based on a similar approach, Terada and co-workers recently proposed a methodology in which chiral phosphoric acid promote the addition of nitrogen based nucleophiles towards alkenyl benzimidazoles (Scheme 6).[12]
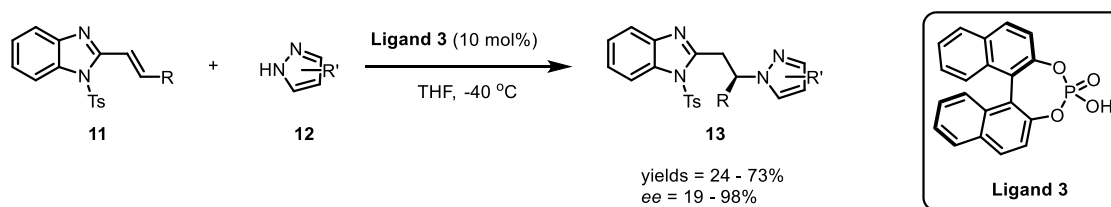
Scheme 6: Aza-Michael type addition to alkenyl benzimidazoles.

Addition of BF$_3$·Et$_2$O in the reaction mixture at -78 °C (Table 1, entry 3) disappointingly did not promote the desired reaction. To our great delight, the introduction of chiral diphosphine ligand **L1** in the system led to the formation of desired product **14a** in moderate yield and good enantioselectivity (Table 1, entry 4). An operational temperature below -50 °C is necessary since at higher temperatures the reaction between the BF$_3$·Et$_2$O and the Grignard reagent become predominant. Considering that no reaction is taking place in absence of the chiral catalyst, the stereocontrol of the process will be determined exclusively by the catalyst ability to transfer the chiral information.

Table 1: Preliminary studies on the addition of EtMgBr to compound **10a**.
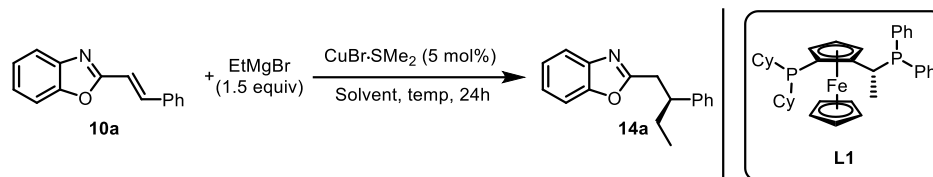
Entry	L	Solvent	Additive (1.5 equiv)	Temp. [°C]	Yield (%)[a]	ee (%)[b]
1	-	tBuOMe	-	-25	Complex mix.	-
2	**L1**	tBuOMe	-	-25	Complex mix.	-
3	-	Toluene	BF$_3$·OEt$_2$	-78	0	-
4	**L1**	Toluene	BF$_3$·OEt$_2$	-78	59	87

[a] Reported yields are for isolated products; [b] Determined by chiral HPLC.

Having found BF$_3$·Et$_2$O able to promote the reaction, the effect of different organic solvents and chiral ligands was assessed (Table 2). In almost every solvent tested, the desired addition product **14a** was obtained with excellent levels of stereocontrol and good to excellent yields. The only exception was THF (Table 2, entry 4) that delivered the product in moderate enantioselectivity. Moreover, due to the large amount of side products formed, it was impossible to isolate compound **14a** in a pure form. This outcome can be rationalised taking into account the different reactivity of Grignard reagents depending on their aggregation state in solution. Grignard reagents dissolved in non-coordinating solvents have high aggregation order, existing usually as dimers or trimers.[13] Coordinating solvents, like THF, can break these aggregates forming monomers, that appear to be more reactive than in the aggregate state.[13c] This behaviour can explain the lower selectivity and higher amount of side products when the reaction was run in THF. To continue our investigation, Et$_2$O was chosen as solvent for its superior performance compared to the other solvents tested in our catalytic protocol (Table 3, entry 5).

Table 2: Solvent screening
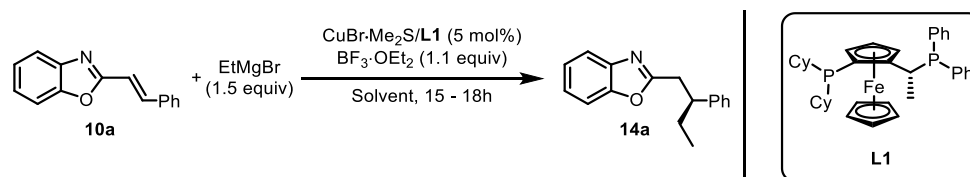
Entry	Solvent	Time [h]	Yield (%)[a]	ee (%)[b]
1	Tol	16	59	87
2	MTBE	18	55	94
3	DCM	18	67	94
4	THF	18	N.D.	50
5	Et$_2$O	15	94	97

[a] Reported yields are for isolated products; [b] Determined by chiral HPLC.

The effect of other LAs on the same transformation was studied next. Trimethylsilyl chloride (TMSCl), TiCl$_4$, MgBr$_2$ and trimethylsilyl trifluoromethansulfonate (TMSOTf) were examined but none of them gave superior results compared with BF$_3$·Et$_2$O (Table 3).

Table 3: Lewis acid screening.

| Entry	L.A.	[Equiv.]	Conv.[%]a	Yield(%)[a]	*ee* (%)[b]
1	TiCl$_4$	1.1	0	-	-
2	TMSCl	1.1	0	-	-
3	MgBr$_2$	1.1	0	-	-
4	TMSOTf[c]	2.0	25	-	-
5	BF$_3$·OEt$_2$	1.1	100	94	97

[a] Reported yields are for isolated products; [b] Determined by chiral HPLC; [c] reaction with 1.2 equivalents of TMSOTf has been carried out in DCM showing only 50% conv. towards the desired product. Reaction condition: 0.1 mmol of **10a**, CuBr·Et$_2$O 5 mol%, **L1** 6 mol%, Lewis acid, EtMgBr 1.5 equiv., Et$_2$O 1ml, -78 °C.

For the optimization of the catalytic system, different phosphine ligands were studied. Binaphthyl bidentate ligand **L4** and **L5** delivered the product with enantioselectivity above 90% but with moderate yields (Table 4, entries 4 and 5). On the other hand, monodentate phosphoramidite ligands **L6** and **L7** failed in promoting the reaction and unreacted starting material was recovered (Table 4, entries 6 and 7). Ferrocenyl ligand **L3**, belonging to the Josiphos family, delivered product **14a** with moderate yield and enantioselectivity (Table 4, entry 3). Ligand **L2** did not catalysed the reaction probably due to the sterically demanding substituent. Several bidentate diphosphine ligands are able to promote the desired reaction, however due to the higher yield obtained, ligand **L1** was selected as optimal ligand. Once the optimal reaction conditions were established (0.1 mmol of **10a**, CuBr·SMe$_2$ 5 mol%, **L1** 6 mol%, BF$_3$·OEt$_2$ 1.1 equiv, EtMgBr 1.5 equiv, Et$_2$O 1ml, -78 °C), the effect of various substituents on the phenyl ring at the β-position of the double bond was investigated (Scheme 7). In all the cases, regardless the electronic properties of the substituent, the addition products **14b** – **14h** were obtained with high enantioselctivities. However, the reactivity of the substrates showed to be strongly dependent on the nature of the substituents. The corresponding addition products were obtained with a broad range of yields without a clear trend (Scheme 7). The aromatic β-substituent can be replaced by an alkyl chain furnishing the corresponding product in good yield and enantioselectivity (Scheme 7, compound **2h**).

Table 4: Chiral ligand screening.
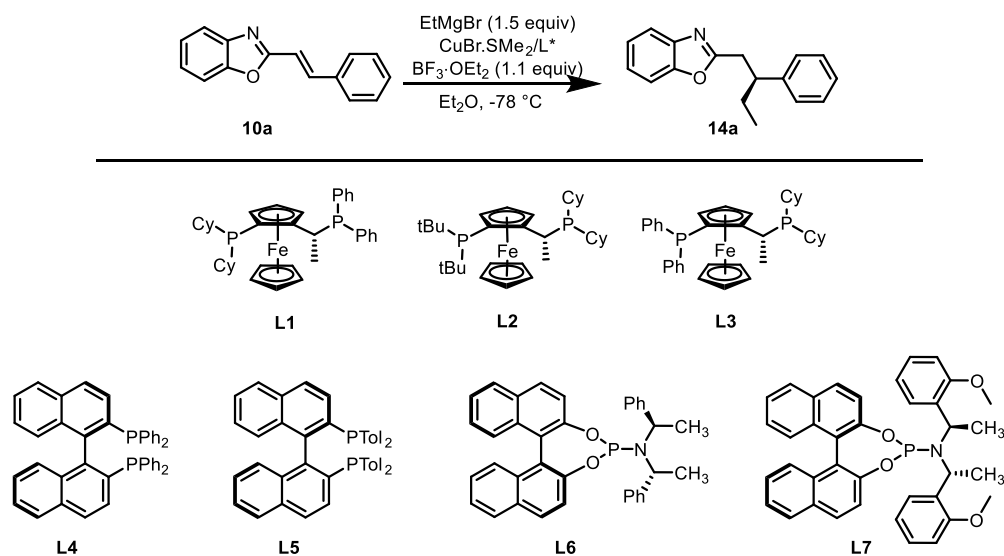
| Entry	Ligand	Cat [%]	Solvent	Time [h]	Yield (%)[a]	ee (%)[b]
1	L1	5	Et_2O	15	94	97
2	L2	10	Et_2O	15	-	-
3	L3	10	Et_2O	15	35	53
4	L4	10	Tol[c]	19	36	91
5	L5	5	Tol[c]	18	45	92
6	L6	10	Tol[c]	19	-	-
7	L7	10	Et_2O	15	-	-

[a] Reported yields are for isolated products; [b] Determined by chiral HPLC; [c] Toluene was used instead of Et_2O due to the insolubility of the ligand in ethereal solvent.
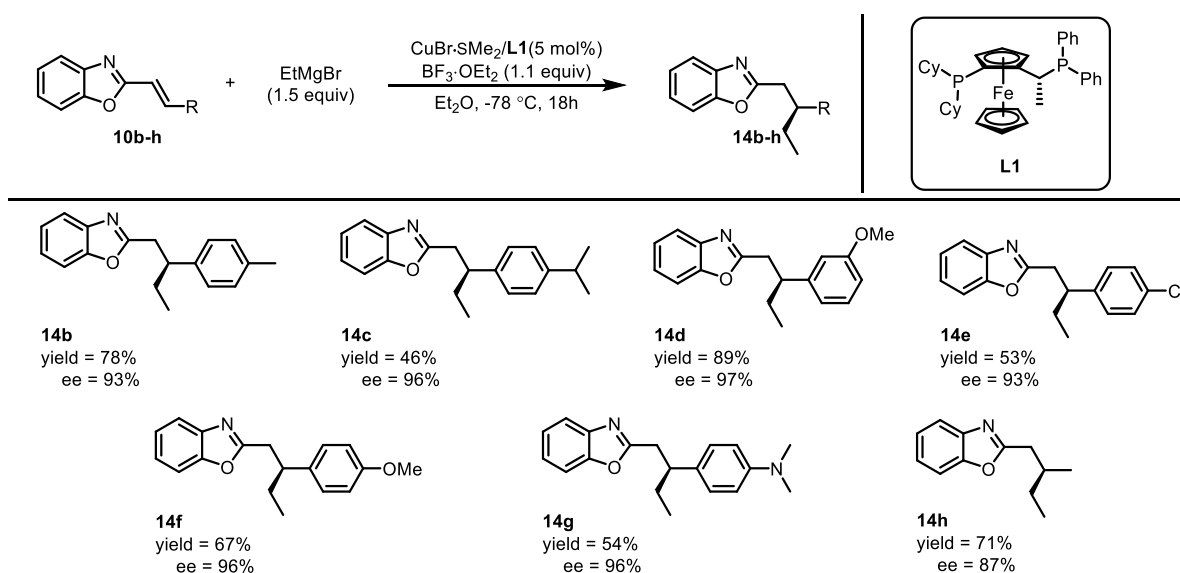
Scheme 7: Influence of different substituents at β-position. [a] Reported yields are for isolated products; [b] Determined by chiral HPLC; [c] Absolute configuration was assigned by analogy with the literature.[14]

The substrate scope was investigated by evaluating the reactivity of other naturally occurring heteroaromatic moieties.[1] For our delight not only benzoxazole, but also other heteroaromatic

substrates such as benzothiazoles (**10i** and **10j**), oxazoles (**10k** and **10l**), pyrimidines (**10m** and **10n**), triazine (**10o**) and quinoline (**10p**), underwent conjugate addition of EtMgBr smoothly. The corresponding products were isolated with high yields and enantioselectivities (Scheme 8). When 4-styryl pyridine **10q** was subjected to our protocol, no conversion to the corresponding addition product **14q** was detected. Further studies that will be discussed in the next chapter will show that pyridine-based substrates require different reaction condition in order to undergo conjugated addition with high level of stereocontrol and yields.
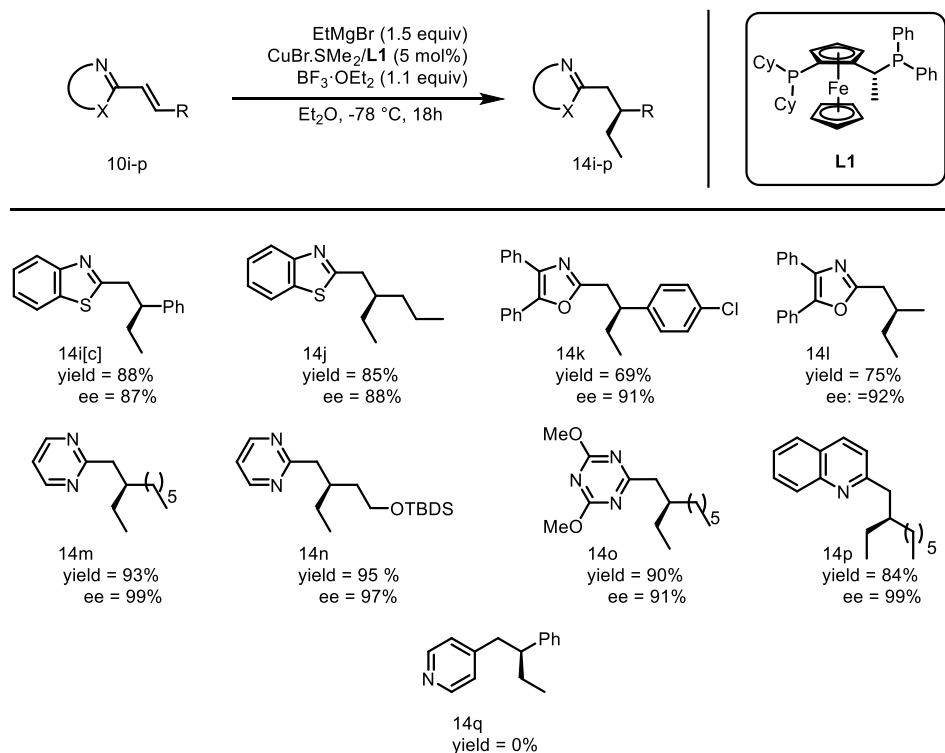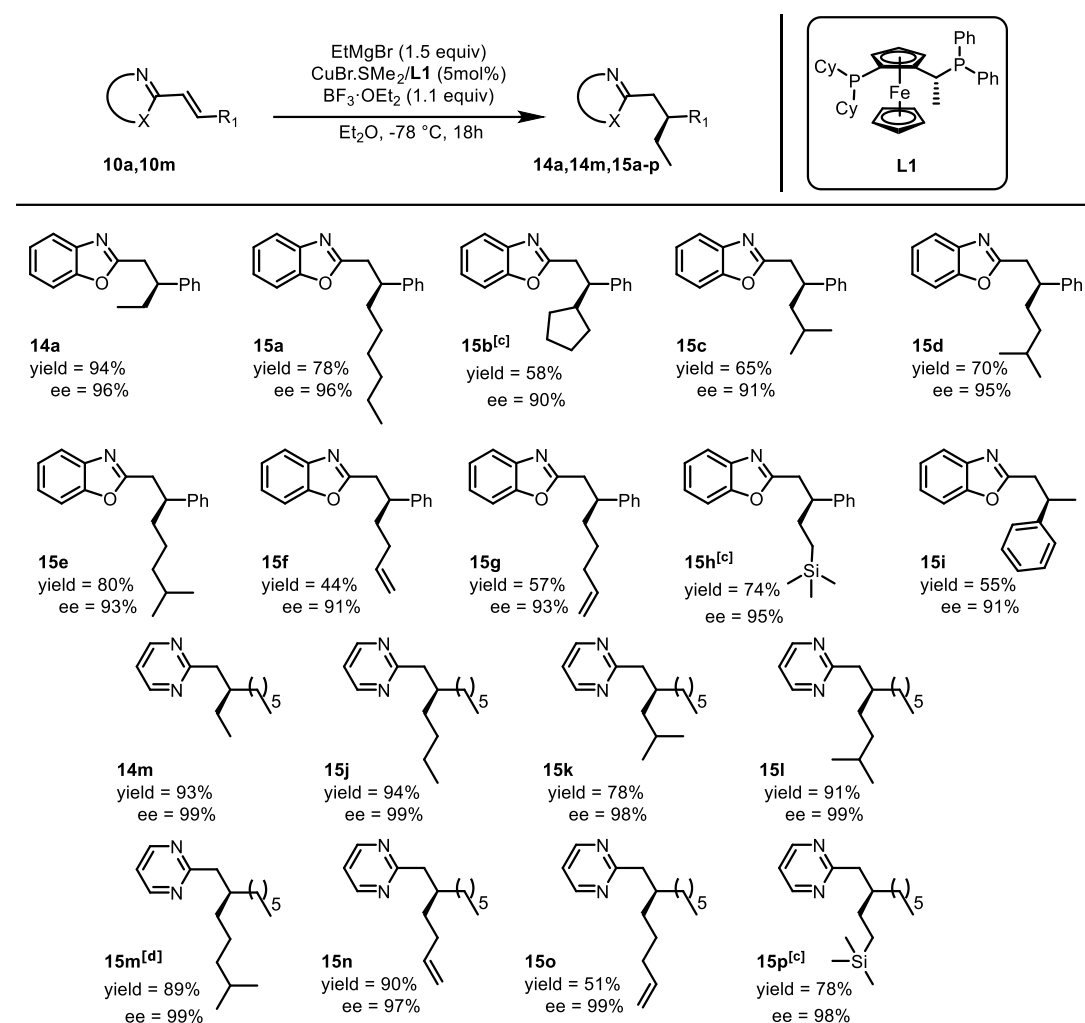

Scheme 8: Aromatic heterocycles scope. [a] Reported yields are for isolated products; [b] Determined by chiral HPLC; [c] 3 equiv of EtMgBr and 2.2 equiv of BF$_3$·Et$_2$O were used in this case.

This insensitivity to the nature of the hetero-aromatic moiety, which might be expected to interfere with the stability and activity of the chiral copper catalyst, makes the reaction remarkably general.

Next, the scope of the nucleophiles was assessed and for this purpose two different aromatic heterocycles, benzoxazole **10a** and pyrimidine **10m**, were selected. Aliphatic, both linear and branched, as well as cyclic, functionalized and aromatic Grignard reagents were studied as nucleophiles. In the case of compound **10a**, all the corresponding addition products were isolated with enantioselectivities around 90% while the yields were from good to excellent, with only few exceptions in which the yields were moderate (Scheme 9, **15b**, **15f**, **15i**, **15o**). Chain length did not influenced strongly the process (Scheme 9, compound **14a** *vs* **15a**) while the system showed to be sensitive to the steric hindrance of the nucleophile. This trend is reflected in the isolated yields of compounds **15b** to **15e:** less hindered the nucleophile, higher the yield. Grignard reagents bearing a terminal olefin or trimethylsylyl moiety were also tolerated, delivering the product with moderate to good yields. Addition of PhMgBr led to the desired product in moderate yield but with excellent stereocontrol (Scheme 9, compound **3i**). When substrate **10m** was tested with the same nucleophiles, the process exhibited comparatively superior stereocontrol. In all the cases, the corresponding addition product was obtained with enantioselectivities above 97%. On the other hand, **10m** has demonstrated to be more sensitive

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to bulky nucleophiles. In this case, addition of sterically demanding α-branched Grignard reagents (i.e. *c*-pentyl-MgBr, PhMgBr) was not possible.
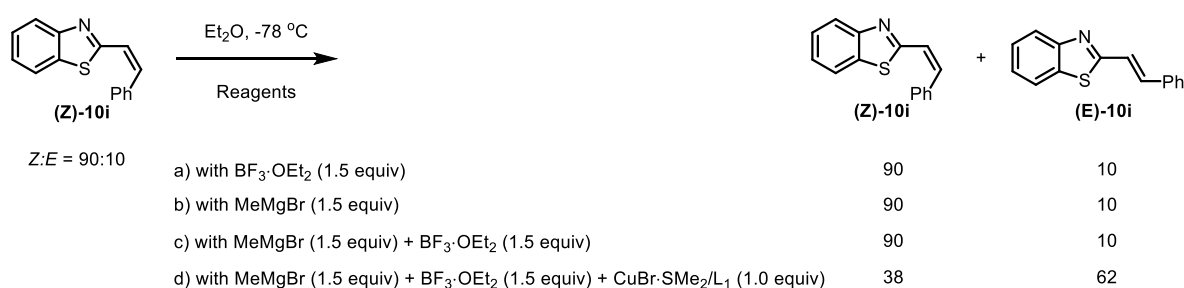

Scheme 9: Grignard reagents scope. [a] Reported yields are for isolated products; [b] Determined by chiral HPLC; [c] 3equiv of EtMgBr and 2 equiv of BF$_3$·Et$_2$O were used in this case; [d]solvent mixture Et$_2$O/DCM (2:1) was used in this case.

Substrate **10m** was also subjected to a series of experiment to determine the feasibility of the scaling up of the reaction. Reducing the catalyst loading to 1mol% did not affect the reaction outcome as well as running the reaction in a larger 10-fold scale. In both cases, the product was obtained without any loss in terms of yield and enantioselectivity. Moreover, the copper catalyst recovered from the latter reaction can be reused in a new reaction maintaining its efficiency (Scheme 10).
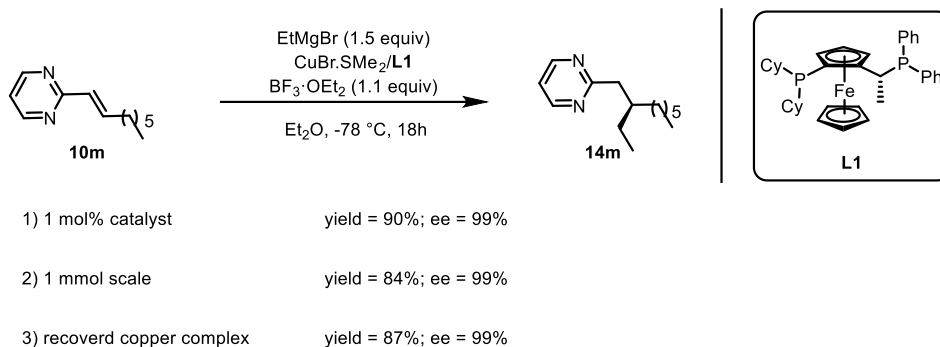
Scheme 10: Scale up experiments.

It is known that in asymmetric reactions involving alkenes transformation, the configuration of the double bond has a substantial influence on the steriodetermination of the reaction product.[13] In their mechanistic studies on ACA of Grignard reagents to enones and enoates, Harutyunyan *et al.* showed that moving from *trans* to *cis* double bond configuration in the copper catalysed ACA to enoates, led to the formation of the corresponding addition product with opposite absolute configuration and lower enantioselectivity.[13] Further studies proved that under their reaction conditions, isomerization of the *cis* double bond towards the more stable *trans* took place explaining the loss in enantioselectivity. In order to investigate the influence of the geometry of the double bond over the stereoselectivity in our system, the addition of EtMgBr to (*Z*)-2-styrylbenzothioazole **(Z)-10i** was performed. Compound **(Z)-10i** was prepared in 90% purity by isomerization of **(E)-10i** using ultraviolet light irradiation. Similarly to the abovementioned results, subjecting **(Z)-10i** to our standard reaction conditions led to the formation of the corresponding addition product **14i** with opposite absolute configuration but drastically lower enantioselectivity (40% ee *vs* 86% ee). Also in this case, the drop in the stereocontrol could be ascribed to partial isomerization of the substrates during the reaction promoted by the active catalyst. In order to confirm this hypothesis, the addition of EtMgBr to compound **(Z)-10i** in our standard condition was monitored by NMR spectroscopy. Unfortunately, the high rate of the reaction prevented the analysis of the reaction mixture in real time. The use of the less reactive MeMgBr, with which no addition to **(Z)-10i** occurs, allowed us to monitor the process via NMR spectroscopy. Several experiment with different combination of reaction components were carried out pointing that isomerization of the double bond indeed took place but only when CuBr·SMe$_2$, **L1**, BF$_3$·OEt$_2$ and MeMgBr were present in the reaction media (Scheme 11).

|	(Z)-10i	(E)-10i
a) with BF$_3$·OEt$_2$ (1.5 equiv)	90	10
b) with MeMgBr (1.5 equiv)	90	10
c) with MeMgBr (1.5 equiv) + BF$_3$·OEt$_2$ (1.5 equiv)	90	10
d) with MeMgBr (1.5 equiv) + BF$_3$·OEt$_2$ (1.5 equiv) + CuBr·SMe$_2$/L$_1$ (1.0 equiv)	38	62

Scheme 11: Isomerization experiments

Extensive NMR studies on the CA of stoichiometric amount of organocuprates to enones and enoates conducted by Ogle,[15] have detected key intermediates in the process. Organocuprates form a Cu(I) π-complex with the C-C double bond of the substrates that evolve in a Cu(III) σ-complex upon oxidative addition (Scheme12).

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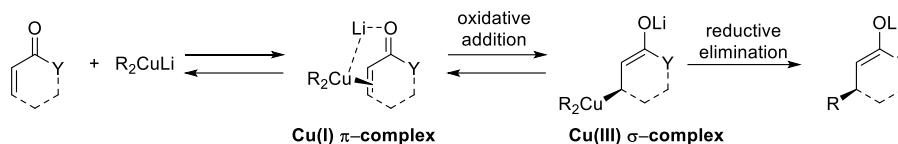
Scheme 12: Reaction mechanism for the CA of organocuprates to enones and enoates.

Assuming that the mechanism depicted above could represent a single catalytic cycle, the double bond isomerization reaction observed for CA to enoates, suggests that the Cu(I) π-complex is in fast equilibrium with the Cu(III) σ-complex. Based on the analogies between the CA to enoates[13,15] and our system, it is plausible that the latter follows a similar mechanism (Scheme 13).
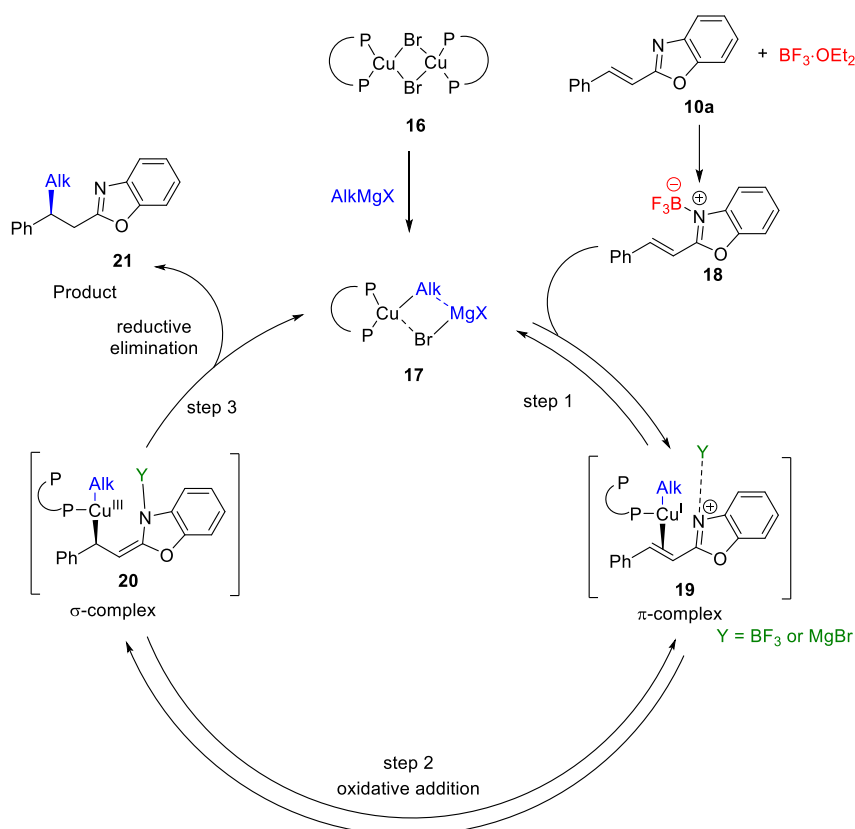
Scheme 13: Tentative mechanism for the asymmetric copper catalysed CA of Grignard reagents to alkenyl aromatic heterocycles.

The process starts with the formation of catalytically active species **17** upon transmetallation of Cu/diphosphine dimeric complex by a molecule of Grignard reagent. Complex **17** then will form π-complex **19** after reaction whit the activated substrate **18** (Scheme 13, step1). Oxidative addition process (Scheme 13, step 2) lead to the formation of σ-complex **20**. Finally, reductive elimination (Scheme 13, step 3) affords product **21** and restores active species **17**.

2.3 Conclusion

In summary, a simple methodology for remote functionalization of several aromatic heterocycles has been developed. Combination of highly reactive and readily available Grignard reagents, copper-diphosphine chiral complexes and boron based Lewis acid additives has shown to be an extremely efficient tool to overcame the low reactivity of the heteroaromatic substrates allowing the introduction of aliphatic substituents, that was not possible with the known methodologies.

Furthermore, this transformation can be carried out in the most common organic solvent, such as dichloromethane, diethyl ether, toluene and methyl tert-butyl ether with the latter two commonly used for industrial process. The necessity of using pricy ferrocenyl diphosphine ligands in our protocol it is compensated by the fact that the copper-diphosphine chiral complexes can be recovered without loss in the efficiency. Mechanistic studies aimed to clarify the role of the Lewis acid and achieve a deeper comprehension of the reaction mechanism are underway.

2.4 Experimental Section

2.4.1 General Information

All reactions using oxygen- and/or moisture-sensitive materials were carried out with anhydrous solvents (*vide infr*a) 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 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), 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: 77.00 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, quin: quintet, sex: sextet, sep: septet, m: multiplet). Exact mass spectra were recorded on a LTQ Orbitrap XL apparatus with ESI ionization. Enantiomeric excesses were determined by Chiral HPLC analysis using a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector. *E-Z* photoisomerization experiments were performed using Spectroline model ENC-280C/FE lamp (λ_{max} = 365 nm, ± 30nm). 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 (EtMgBr, PhMgBr (3M in Et$_2$O), ButMgBr, HexMgBr, *i*PentMgBr, *i*ButMgBr, 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. (*i*HexMgBr (1.5 M in Et$_2$O), but-3-en-1-ylMgBr (1.2M in Et$_2$O), pent-4-en-1-ylMgBr (1.5M in Et$_2$O) and TMS(CH$_2$)$_2$MgBr (0.4 M in Et$_2$O). Unless otherwise noted substrates were prepared by literature reported methods (*vide infra*). Chiral ligands (**L1-L7**) 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. Absolute configuration of the chiral compounds were determined by analogy with literature report (*vide infra*).[14]

2.4.2 Synthesis and Characterizations of Substrates

(*E*)-2-styrylbenzoxazole (10a)[16]
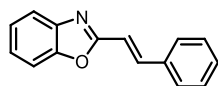
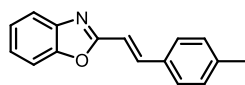

Compound **10a** was prepared by literature procedure.[7] The product was obtained as a white solid after crystallization in MeOH.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.74 (d, *J* = 16.3 Hz, 1H), 7.68-7.64 (m, 1H), 7.54 (m, 2H), 7.51-7.45 (m, 1H), 7.39-7.25 (m, 5H), 7.02 (d, *J* = 16.3 Hz, 1H).

13C NMR (101 MHz, CDCl₃): δ 162.8, 150.4, 142.1, 139.5, 135.1, 129.8, 129.0, 127.6, 125.2, 124.5, 119.8, 113.9, 110.3.

(*E*)-2-(4-methylstyryl)benzoxazole (10b)[17]

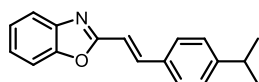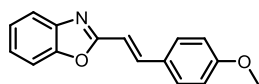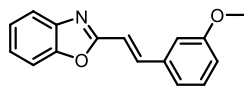Compound **1b** was prepared by literature procedure.[3b] The product was obtained as a white solid after crystallization in MeOH.

1H NMR (400 MHz, CDCl₃): δ 7.77 (d, *J* = 16.3 Hz, 1H), 7.74 – 7.68 (m, 1H), 7.55 – 7.46 (m, 3H), 7.36 – 7.29 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 16.3 Hz, 1H), 2.39 (s, 3H).

13C NMR (101 MHz, CDCl₃): δ 163.0, 150.4, 142.2, 140.2, 139.5, 132.4, 129.7, 127.5, 125.1, 124.4, 119.7, 112.8, 110.3, 21.5.

(*E*)-2-(4-isopropylstyryl)benzoxazole (10c)

Compound **1c** was prepared by literature procedure.[3b] The product was obtained as a white solid after crystallization in MeOH. Yield = 45%.

1H NMR (400 MHz, CDCl₃): δ 7.75 (d, *J* = 16.3 Hz, 1H), 7.67 (dt, *J* = 7.5, 3.7 Hz, 1H), 7.53 – 7.43 (m, 3H), 7.33 – 7.20 (m, 4H), 7.01 (d, *J* = 16.3 Hz, 1H), 2.90 (sep, *J* = 7.0 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H).

13C NMR (101 MHz, CDCl₃): δ 163.0, 151.1, 150.4, 142.2, 139.5, 132.8, 127.7, 127.1, 125.1, 124.5, 124.1, 119.7, 112.9, 110.3, 34.1, 23.8.

HR-MS (EI): *m/z* calcd. for $C_{18}H_{17}N_1O_1$ ([M+H⁺]) 264.13829, found 264.13798.

(*E*)-2-(4-methoxystyryl)benzoxazole (10d)[3c]

Compound **1d** was prepared by literature procedure.[3b] The product was obtained as a white solid after crystallization in MeOH.

1H NMR (400 MHz, CDCl₃): δ 7.85 (d, *J* = 16.3 Hz, 1H), 7.82 – 7.77 (m, 1H), 7.68 – 7.58 (m, 3H), 7.45 – 7.39 (m, 2H), 7.08 – 7.00 (m, 3H), 3.95 (s, 3H).

13C NMR (101 MHz, CDCl₃): δ 163.1, 160.8, 150.2, 142.1, 139.0, 129.0, 127.8, 124.7 , 124.2, 119.5, 114.3, 111.4, 110.0, 55.2.
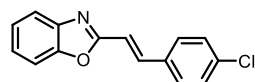
(*E*)-2-(3-methoxystyryl)benzoxazole (10e)[3c]

Compound **1e** was prepared by literature procedure.[3b] The product was obtained as a yellow solid after silica gel flash-chromatography (CH$_2$Cl$_2$:Pentane, 2:1, v/v).

¹H NMR (400 MHz, CDCl$_3$): δ 7.77 – 7.67 (m, 2H), 7.53 – 7.46 (m, 1H), 7.34 – 7.27 (m, 3H), 7.19 – 7.14 (m, 1H), 7.09 (s, 1H), 7.04 (dd, *J* = 16.3, 0.9 Hz, 1H), 6.93 – 6.87 (m, 1H), 3.82 (d, *J* = 1.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl$_3$): δ 176.6, 160.0, 150.4, 142.2, 139.4, 136.5, 129.9, 125.2, 124.5, 120.2, 119.9, 115.6, 114.2, 112.5, 110.3, 55.3.

(*E*)-4-(2-(benzoxazol-2-yl)vinyl)-N,N-dimethylaniline (10f)[18]
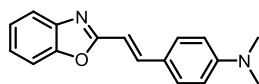
Compound **1f** was prepared by literature procedure.[3b] The product was obtained as an orange solid after crystallization in MeOH.

¹H NMR (400 MHz, CDCl$_3$): δ 7.69 (d, *J* = 16.2 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.49 – 7.41 (m, 3H), 7.29 – 7.23 (m, 2H), 6.81 (d, *J* = 16.2, 1.7 Hz, 1H), 6.68 (d, *J* = 8.9 Hz, 2H), 2.99 (s, 6H).

¹³C NMR (101 MHz, CDCl$_3$): δ 164.0, 150.3, 142.4, 139.9, 129.1, 124.4, 124.2, 119.3, 112.0, 110.0, 108.5, 40.2.
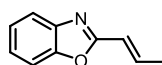
(*E*)-2-(4-chlorostyryl)benzoxazole (10g)[3c]

Compound **1g** was prepared by literature procedure.[3b] The product was obtained as a white solid after crystallization in MeOH.

¹H NMR (400 MHz, CDCl$_3$): δ 7.70 – 7.61 (m, 2H), 7.48 – 7.39 (m, 3H), 7.34 – 7.29 (m, 2H), 7.29 – 7.23 (m, 2H), 6.96 (d, *J* = 16.3 Hz, 1H).

¹³C NMR (101 MHz, CDCl$_3$): δ 162.4, 150.4, 142.1, 138.0, 135.6, 133.6, 129.2, 128.7, 125.4, 124.6, 119.9, 114.5, 110.3.

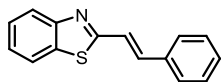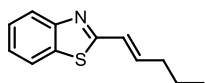**(*E*)-2-(prop-1-en-1-yl)benzoxazole (10h)[19]**

Compound **1h** was prepared by literature procedure.[20] The product was obtained as a pale-yellow solid after silica gel chromatography (Pentane: EtOAC, 95:05, v/v).

1H NMR (400 MHz, CDCl$_3$): δ 7.75 – 7.59 (m, 1H), 7.55 – 7.40 (m, 1H), 7.35 – 7.20 (m, 2H), 7.04 (dq, J = 15.9, 6.9 Hz, 1H), 6.46 (dq, J = 15.9, 1.8 Hz, 1H), 2.02 (dd, J = 6.9, 1.8 Hz, 3H).

13C NMR (101 MHz, CDCl$_3$): δ 162.3, 150.1, 141.9, 139.0, 124.7, 124.2, 119.7, 118.2, 110.1, 18.7.

(*E*)-2-styrylbenzothiazole (10i)[3a]

Compound **1i** was prepared by literature procedure.[3b] The product was obtained as a white solid after crystallization in MeOH.

1H NMR (400 MHz, CDCl$_3$): δ 8.01 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.54 (d, J = 16.2 Hz, 1H), 7.48 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.45 – 7.34 (m, 5H).

13C NMR (101 MHz, CDCl$_3$): δ 137.7, 129.4, 128.9, 127.4, 126.3, 125.3, 122.9, 122.1, 121.5.

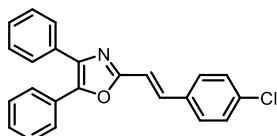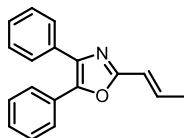### (*E*)-2-(pent-1-en-1-yl)benzothiazole (10j)[21,22]

Compound **1j** was prepared by literature procedure.[21] The product was obtained as orange yellow solid after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v).

1H NMR (400 MHz, CDCl$_3$): δ 7.93 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 9.3 Hz, 1H), 7.39 (td, J = 8.3, 7.2, 1.3 Hz, 1H), 7.32 – 7.24 (m, 1H), 6.80 – 6.63 (m, 2H), 2.28 – 2.13 (m, 2H), 1.52 (sex, J = 7.4 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H).

13C NMR (101 MHz, CDCl$_3$): δ 167.3, 153.5, 141.7, 133.9, 125.9, 124.9, 124.6, 122.6, 121.2, 34.8, 21.6, 13.6.

### (*E*)-2-(4-chlorostyryl)-4,5-diphenyloxazole (10k)[23]

Compound **1k** was prepared by literature procedure.[23] The product was obtained as pale yellow solid after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v).

1H NMR (400 MHz, CDCl$_3$) δ 7.75 – 7.63 (m, 4H), 7.55 (d, J = 16.4 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.44 – 7.29 (m, 8H), 6.99 (d, J = 16.4 Hz, 1H).

13C NMR (101 MHz, CDCl$_3$) δ 159.7, 145.4, 137.0, 134.9, 134.6, 134.1, 132.4, 129.1, 128.8, 128.7, 128.6, 128.3, 128.0, 127.8, 126.6, 114.3.

(E)-4,5-diphenyl-2-(prop-1-en-1-yl)oxazole (10l)[23]

Compound **1l** was prepared by literature procedure.[23] The product was obtained as pale yellow solid after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v).

1H NMR (400 MHz, CDCl$_3$) δ 7.81 – 7.67 (m, 2H), 7.67 – 7.56 (m, 2H), 7.49 – 7.21 (m, 6H), 6.85 (dq, J = 15.8, 6.9 Hz, 1H), 6.41 (d, J = 15.8 Hz, 1H), 1.96 (dd, J = 6.9, 1.8 Hz, 3H).

13C NMR (101 MHz, cdcl$_3$) δ 159.8, 144.6, 136.1, 135.4, 132.6, 129.0, 128.6, 128.5, 128.4, 128.1, 128.0, 126.5, 117.8, 18.6.

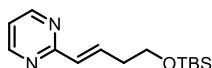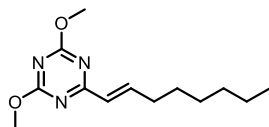## (E)-2-(oct-1-en-1-yl)pyrimidine (10m)[24]
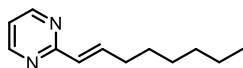
Compound **1m** was prepared by literature procedure.[24] The product was obtained as colorless oil after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v).

1H NMR (400 MHz, CDCl$_3$): δ 8.65 (d, J = 4.9 Hz, 2H), 7.17 (dt, J = 15.6, 7.0 Hz, 1H), 7.05 (t, J = 4.9 Hz, 1H), 6.55 (dt, J = 15.6, 1.5 Hz, 1H), 2.30 (qd, J = 7.2, 1.6 Hz, 2H), 1.57 – 1.44 (m, 2H), 1.42 – 1.20 (m, 6H), 0.93 – 0.79 (m, 3H).

13C NMR (101 MHz, CDCl$_3$): δ 164.8, 156.9, 142.5, 129.4, 118.3, 32.7, 31.7, 28.9, 28.6, 22.6, 14.1.

(E)-2-(4-((tert-butyldimethylsilyl)oxy)but-1-en-1-yl)pyrimidine (10n)[25]
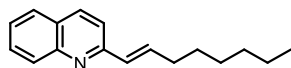

Compound **1n** was prepared by literature procedure.[24] The product was obtained as colorless oil after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v).

1H NMR (400 MHz, CDCl$_3$): δ 8.47 (d, J = 4.8 Hz, 2H), 6.99 (dt, J = 15.0, 7.2 Hz, 1H), 6.88 (t, J = 4.9 Hz, 1H), 6.44 (d, J = 15.7 Hz, 1H), 3.61 (t, J = 6.9 Hz, 2H), 2.36 (q, J = 6.9 Hz, 2H), 0.72 (s, 9H), -0.11 (s, 6H).

13C NMR (400 MHz, CDCl$_3$): δ 164.5, 156.9, 138.2, 131.2, 118.4, 62.2, 36.3, 25.9, 18.3 -5.3.

## (E)-2,4-dimethoxy-6-(oct-1-en-1-yl)-1,3,5-triazine (10o)

Compound **1o** was prepared by literature procedure.[24] The product was obtained as colorless oil after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v).

¹H NMR (400 MHz, CDCl₃): δ 7.36 (dt, J = 15.5, 7.0 Hz, 1H), 6.27 (d, J = 15.5 Hz, 1H), 3.98 (s, 6H), 2.29 – 2.18 (m, 2H), 1.45 (quin, J = 7.2 Hz, 2H), 1.35 – 1.15 (m, 6H), 0.87 – 0.76 (m, 3H).

¹³C NMR (101 MHz, CDCl₃): 174.8, 172.5, 147.7, 127.8, 54.9, 32.7, 31.6, 28.9, 28.2, 22.5, 14.0.

HRMS (ESI⁺): m/z calcd. for $C_{13}H_{21}N_3O_2$ ([M+H⁺]) 252.17065, found 252.17052.

(*E*)-2-(oct-1-en-1-yl)quinolone (10p)[26]

Compound **1p** was prepared by literature procedure.[24] The product was obtained as colorless oil after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v).

¹H NMR (400 MHz, CDCl₃): δ 8.10 – 7.95 (m, 2H), 7.76 – 7.59 (m, 2H), 7.55 – 7.34 (m, 2H), 6.90 – 6.76 (m, 1H), 6.70 (d, J = 15.9 Hz, 1H), 2.30 (q, J = 7.2 Hz, 2H), 1.52 (quin, J = 7.3 Hz, 2H), 1.42 – 1.19 (m, 6H), 0.97 – 0.79 (m, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 156.5, 148.0, 138.0, 136.1, 131.0, 129.5, 129.1, 127.4, 127.1, 125.8, 118.7, 33.1, 31.7, 29.0, 28.9, 22.6, 14.1.

(*E*)-4-styrylpyridine (10q)
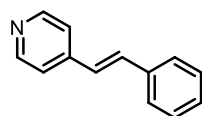
To a heated solution of DMF , KOH (60 °C) and γ-picoline (50 mmol, 1 equiv), benzaldehyde (25mmol, 0.5 equiv) is added dropwise. The reaction mixture is heated to 160 °C. After 16h the reaction mixture is cooled at R.T. and diluted with H_2O. The reaction mixture is extracted with DCM (3x20 ml). The organic phase is washed several times with a fresh portion of H_2O (6x15ml). The combined organic phase are and dried over MgSO₄ and volatiles are removed under reduced pressure. The residue is purified by flash chromatography (80:20 Pentane:EtOAc) and the pure product **10q** is obtained as a white solid. Yield = 63%. The NMR data are in agreement with the one present in literature.[27]

¹H NMR (400 MHz, CDCl₃) 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).

¹³C NMR (101 MHz, CDCl₃) δ 150.3, 144.8, 136.3, 133.3, 129.0, 128.9, 127.2, 126.1, 121.0.

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

2.4.3 General Procedure A: Cu-Catalyzed Asymmetric Grignard Addition to *N*-Containing Aromatic Heterocycles

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, the CuBr·SMe₂ (5 mol%), and ligand (*R*,*S*ₚ)-**L1** (6 mol%) were dissolved in Et₂O (1mL/0.1mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (0.1 - 0.2 mmol, 1 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C and BF₃·OEt₂ (1.5 equiv) was added followed by RMgX (1.5 equiv). After stirring at -78 °C for 18h, the

reaction was quenched with MeOH (1 mL) followed by saturated aqueous NH_4Cl solution and warmed to RT. Reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic phases were dried over $MgSO_4$, filtered and solvents were evaporated on rotary evaporator. The oily crude was purified by flash chromatography on silica using mixture of pentane and EtOAc as eluent.

Notes:

a) Unless otherwise noted all the products were isolated as pale-yellow oil

b) All the reaction outcomes were analyzed after 18h, to accommodate the reaction times required for relatively unreactive substrates. However, we noted that the reaction times for preparing products **14a-h**, **14l, 15a-c**, **15f** and **15g** were distinctly shorter (4h).

c) All the reactions were carried out using 1.5 equiv of Grignard reagents and 1.5 equiv of $BF_3.OEt_2$. However for preparing products **14a-h**, **14l, 15a-c**, **15f** and **15g** the amount of $BF_3.OEt_2$ and RMgX can be reduced to 1.1 equiv and 1.2 equiv respectively.

d) By-product formation derived from formal trapping of the product enolate by the substrate is responsible for relatively lower isolated yields of the following products: **14c, 14d, 14f, 15g, 15e, 15f, 15g, 15i, 15o.**

2.4.4 General Procedure B: Synthesis of Racemic Products.

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, the CuBr·SMe$_2$ (10 mol%), and (±) BINAP (12 mol%) were dissolved in CH_2Cl_2 (1mL/0.1mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (0.1 - 0.2 mmol, 1 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 (1.5 equiv). After stirring at -78 °C for 18h, the reaction was quenched and purified as mentioned above.

(*S*)-2-(2-phenylbutyl)benzoxazole (14a)
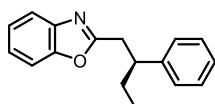
The reaction was performed using general procedure A, with 0.2 mmol **10a**, $BF_3·OEt_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R,S$_p$*)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14a** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 90:10, v/v), [94% yield, 96% ee].

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.72 – 7.56 (m, 1H), 7.55 – 7.38 (m, 1H), 7.36 – 7.11 (m, 7H), 3.42 – 3.06 (m, 3H), 1.93 – 1.58 (m, 2H), 0.81 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101, MHz, CDCl$_3$): δ 167.34, 152.04, 144.9, 129.9, 128.9, 128.0, 125.9, 125.5, 121.0, 111.7, 47.1, 37.3, 30.2, 13.3.

HRMS (ESI$^+$): *m/z* calcd. for $C_{17}H_{17}N_1O_1$ ([M+H$^+$]) 252.13829, found 252.13833.

CSP-HPLC: (237nm, Chiralcel OZ-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), t$_R$ = 29.3 min (major), t$_R$ = 33.1 min (minor).

(*S*)-2-(2-(p-tolyl)butyl)benzoxazole (14b)
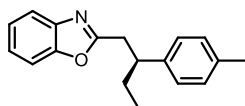
The reaction was performed using general procedure A, with 0.2 mmol **10b**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14b** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 90:10, v/v), [78% yield, 95% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 7.71 – 7.60 (m, 1H), 7.49 – 7.42 (m, 1H), 7.32 – 7.23 (m, 2H), 7.15 – 7.05 (m, 4H), 3.30 – 3.09 (m, 3H), 2.30 (s, 3H), 1.92 – 1.57 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl$_3$) δ 166.0, 150.7, 141.3, 140.4, 136.0, 129.2, 127.3, 124.4, 124.0, 119.5, 110.3, 45.2, 36.0, 28.7, 21.0, 11.9.

HRMS (ESI⁺): *m/z* calcd. for C$_{18}$H$_{19}$NO ([M+H⁺]) 266.15394, found 266.15422.

CSP-HPLC: (254 nm, Chiralcel OD-H, *n*-heptane/*i*-PrOH 98:2, 40 °C, 0.5 ml/min.) t$_R$ = 12.6 min (major), t$_R$ =13.5 min (minor).

(*S*)-2-(2-(4-isopropylphenyl)butyl)benzoxazole (14c)
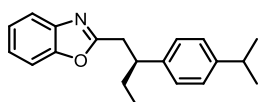
The reaction was performed using general procedure A, with 0.2 mmol **10c**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14c** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 90:10, v/v), [46% yield, 96% ee].

**¹H NMR** (400 MHz, CDCl$_3$) δ 7.76 – 7.59 (m, 1H), 7.51 – 7.39 (m, 1H), 7.38 – 7.22 (m, 2H), 7.15 (s, 4H), 3.33 – 3.10 (m, 3H), 2.87 (hept, *J* = 6.9 Hz, 1H), 1.94 – 1.55 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 6H), 0.81 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl$_3$) δ 166.1, 150.7, 147.0, 141.3, 140.8, 127.3, 126.5, 124.4, 124.0, 119.5, 110.3, 45.2, 35.9, 33.6, 28.7, 24.0, 11.9.

HRMS (ESI⁺): *m/z* calcd. for C$_{20}$H$_{23}$NO ([M+H⁺]) 294.18524, found 294.18530.

CSP-HPLC: (254 nm, Chiralcel OZ-H, n-heptane/iPrOH = 99:1, 40 °C, 0.5 ml/min.), t$_R$ = 11.8 min (major), t$_R$ = 12.3 min (minor).

(*S*)-2-(2-(4-methoxyphenyl)butyl)benzoxazole (14d)
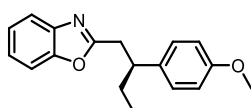
The reaction was performed using general procedure A, with 0.2 mmol **10d**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand

(*R,S*ₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14d** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 93:07, v/v), [67% yield, 95% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 7.70 – 7.55 (m, 1H), 7.53 – 7.38 (m, 1H), 7.33 – 7.19 (m, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 3.76 (s, 3H), 3.35 – 3.03 (m, 3H), 1.87 – 1.54 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl$_3$) δ 166.4, 158.5, 151.0, 141.6, 135.8, 128.7, 124.7, 124.4, 119.9, 114.2, 110.6, 55.5, 45.2, 36.5, 29.3, 12.2.

HRMS (ESI⁺): *m/z* calcd. for C$_{18}$H$_{20}$N$_1$O$_2$ ([M+H⁺]) 282.14886, found 282.14894.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 98:2, 40 °C, 0.5 ml/min.), t$_R$ = 18.0 min (major), t$_R$ = 19.7 min (minor).

(*S*)-2-(2-(3-methoxyphenyl)butyl)benzoxazole (14e)
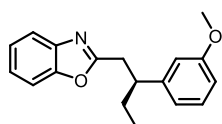
The reaction was performed using general procedure A, with 0.2 mmol **10e**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R,S*ₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14e** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 90:10, v/v), [89% yield, 97% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 7.73 – 7.60 (m, 1H), 7.53 – 7.39 (m, 1H), 7.36 – 7.24 (m, 2H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.88 – 6.81 (m, 1H), 6.80 – 6.70 (m, 2H), 3.76 (s, 3H), 3.33 – 3.13 (m, 3H), 1.88 – 1.63 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl3) δ 165.9, 159.6, 150.7, 145.2, 141.3, 129.5, 124.4, 124.1, 119.8, 119.6, 113.4, 111.7, 110.3, 55.1, 45.7, 35.9, 28.6, 11.9.

HRMS (ESI⁺): *m/z* calcd. for C$_{18}$H$_{19}$NO$_2$ ([M+H⁺]) 282.14886, found 282.14863.

CSP-HPLC: (230 nm, Chiralcel AD-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), t$_R$ = 29.0 min (major), t$_R$ = 34.0 min (minor).

(*S*)-4-(1-(benzo[d]oxazol-2-yl)butan-2-yl)-N,N-dimethylaniline (14f)
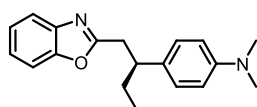
The reaction was performed using general procedure A, with 0.2 mmol **10f**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R,S*ₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14f** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 90:10, v/v), [54% yield, 95% ee].

¹H NMR (400 MHz, CDCl₃) δ 7.71 – 7.59 (m, 1H), 7.52 – 7.41 (m, 1H), 7.34 – 7.22 (m, 2H), 7.10 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 3.30 – 3.06 (m, 3H), 2.90 (s, 6H), 1.85 – 1.57 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 166.3, 150.72, 149.2, 141.4, 131.5, 128.0, 124.3, 123.9, 119.5, 112.8, 110.2, 44.7, 40.7, 36.2, 28.8, 11.9.

HRMS (ESI⁺): m/z calcd. for $C_{19}H_{23}N_2O_1$ ([M+H⁺]) 295.18049, found 295.18048.

CSP-HPLC: (234 nm, Chiralcel OD-H, n-heptane/iPrOH = 98:2, 40 °C, 0.5 ml/min.), t_R = 17.6 min (major), t_R = 18.5 min (minor).

(*S*)-2-(2-(4-chlorophenyl)butyl)benzoxazole (14g)
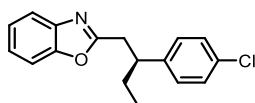
The reaction was performed using general procedure A, with 0.2 mmol **10g**, BF₃·OEt₂ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et₂O, 0.3 mmol, 1.5 equiv), CuBr·SMe₂ (0.01 mmol, 5 mol%), ligand (*R*,*S*ₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et₂O. Product **14g** was obtained as pale-yellow oil after column chromatography (SiO₂, pentane:EtOAc 90:10, v/v), [53% yield, 95% ee].
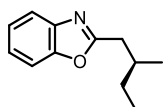
¹H NMR (400 MHz, CDCl₃) δ 7.70 – 7.58 (m, 1H), 7.48 – 7.40 (m, 1H), 7.33 – 7.20 (m, 4H), 7.16 – 7.12 (m, 2H), 3.30 – 3.06 (m, 3H), 1.89 – 1.60 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 141.9, 132.2, 128.8, 128.6, 124.5, 124.1, 119.6, 110.3, 45.0, 35.7, 28.8, 11.8.

HRMS (ESI⁺): m/z calcd. for $C_{17}H_{16}ClNO$ ([M+H⁺]) 286.09932, found 286.09925.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 98:2, 20 °C, 0.5 ml/min.), t_R = 16.4 min (major), t_R = 17.9 min (minor).

(*S*)-2-(2-methylbutyl)benzoxazole (14h)

The reaction was performed using general procedure A, with 0.2 mmol **10h**, BF₃·OEt₂ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et₂O, 0.3 mmol, 1.5 equiv), CuBr·SMe₂ (0.01 mmol, 5 mol%), ligand (*R*,*S*ₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et₂O. Product **14h** was obtained as pale-yellow oil after column chromatography (SiO₂, pentane:EtOAc 97:03, v/v), [71% yield, 87% ee].

¹H NMR (400 MHz, CDCl₃) δ 7.78 – 7.58 (m, 1H), 7.54 – 7.41 (m, 1H), 7.35 – 7.22 (m, 2H), 3.02 – 2.62 (m, 2H), 2.15 – 2.00 (m, 1H), 1.47 (m, J = 13.1, 7.4, 5.6 Hz, 1H), 1.39 – 1.24 (m, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 166.8, 150.8, 141.4, 124.3, 124.0, 119.5, 110.2, 35.6, 33.7, 29.3, 19.2, 11.3.

HRMS (ESI⁺): m/z calcd. for $C_{12}H_{16}NO$ ([M+H⁺]) 190.12264, found 190.12244.

CSP-HPLC: (235 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.8:0.2, 40 °C, 0.35ml/min.), t_R = 36.9 min (major), t_R = 41.2 min (minor).

(*R*)-2-(2-ethylpentyl)benzothiazole (14j)
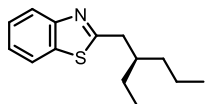
The reaction was performed using general procedure A, with 0.2 mmol **10j**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14j** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 99:01, v/v), [85% yield, 88% ee].

**¹H NMR** (400 MHz, CDCl$_3$) δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 3.04 (d, *J* = 7.2 Hz, 2H), 2.04 – 1.88 (m, 1H), 1.50 – 1.30 (m, 6H), 1.01 – 0.81 (m, 6H).

¹³C NMR (101 MHz, CDCl$_3$) δ 171.7, 153.3, 135.3, 125.8, 124.5, 122.5, 121.4, 40.3, 38.6, 35.2, 25.8, 19.7, 14.3, 10.7.

HRMS (ESI⁺): *m/z* calcd. for C$_{14}$H$_{20}$NS ([M+H⁺]) 234.13110, found 234.13099.

CSP-HPLC: (254 nm, Chiralcel OB-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), t_R = 13.2 min (major), t_R = 18.1 min (minor).

(*S*)-2-(2-(4-chlorophenyl)butyl)-4,5-diphenyloxazole (14k)
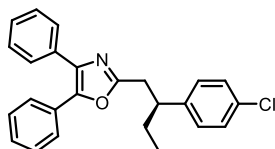
The reaction was performed using general procedure A, with 0.1 mmol **10k**, BF$_3$·OEt$_2$ (0.15 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.15 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.005 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.006 mmol, 6 mol%) in 1mL Et$_2$O. Product **14k** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 98:02, v/v), [69% yield, 91% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 7.66 – 7.53 (m, 2H), 7.51 – 7.43 (m, 2H), 7.41 – 7.23 (m, 8H), 7.22 – 7.11 (m, 2H), 3.26 – 2.96 (m, 3H), 1.93 – 1.59 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H).
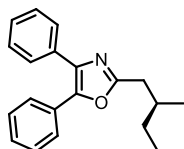
¹³C NMR (101 MHz, cdcl3) δ 161.9, 145.1, 142.2, 135.0, 132.5, 132.1, 129.0, 128.6, 128. 6, 128.5, 128.3, 128.0, 127.9, 126.4, 45.5, 35.4, 28.7, 11.9.

HRMS (ESI⁺): *m/z* calcd. for C$_{25}$H$_{23}$ClNO ([M+H⁺]) 388.14571, found 388.14627.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), t_R = 38.4 min (major), t_R = 41.6 min (minor).

(*S*)-2-(2-methylbutyl)-4,5-diphenyloxazole (14l)

The reaction was performed using general procedure A, with 0.2 mmol **10l**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14l** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 99:01 → 97:03, v/v), [75% yield, 98% ee].

1H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, *J* = 6.7 Hz, 2H), 7.59 (d, *J* = 6.7 Hz, 2H), 7.43 – 7.28 (m, 6H), 2.93 – 2.58 (m, 2H), 2.04 (m, 1H), 1.58 – 1.43 (m, 1H), 1.40 – 1.24 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).

13C NMR (101 MHz, cdcl$_3$) δ 163.2, 145.0, 135.0, 132.7, 129.2, 128.6, 128.5, 128.2, 127.9, 127.9, 126.4, 35.2, 33. 9, 29.3 19.3, 11.3.

HRMS (ESI+): *m/z* calcd. for C$_{20}$H$_{22}$NO ([M+H+]) 292.16959, found 292.16973.

CSP-HPLC: (234 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.8:0.2, 40 °C, 0.5 ml/min.), t$_R$ = 29.5 min (major), t$_R$ = 31.7 min (minor).

(*S*)-2-(2-ethyloctyl)pyrimidine (14m)
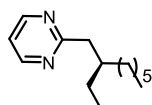
The reaction was performed using general procedure A, with 0.2 mmol **10m**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14m** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 97:03 → 90:10, v/v), [93% yield, 99% ee].

1H NMR (400 MHz, CDCl$_3$) δ 8.66 (d, *J* = 4.9 Hz, 2H), 7.10 (t, *J* = 4.9 Hz, 1H), 2.87 (d, *J* = 1.2 Hz, 2H), 1.99 (m, 1H), 1.50 – 1.06 (m, 12H), 0.86 (m, 6H).

13C NMR (101 MHz, cdcl$_3$) δ 171.5, 156.7, 118.2, 44.0, 39.3, 33.0, 31.8, 29.6, 26.5, 25.9, 22.6, 14.0, 10.7.

HRMS (ESI+): *m/z* calcd. for C$_{14}$H$_{25}$N$_2$ ([M+H+]) 221.20123, found 221.20104.

CSP-HPLC: (254 nm, Chiralcel OZ-H, n-heptane/iPrOH = 99.2:0.8, 40 °C, 0.5 ml/min.), t$_R$ = 17.7 min (minor), t$_R$ = 19.8 min (major).

(S)-2-(4-((tert-butyldimethylsilyl)oxy)-2-ethylbutyl)pyrimidine (14n)
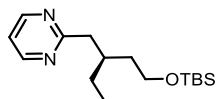
The reaction was performed using general procedure A, with 0.2 mmol **10n**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (R,S$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14n** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 92:08, v/v), [95% yield, 97% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 8.64 (d, J = 4.9 Hz, 2H), 7.09 (t, J = 4.9 Hz, 1H), 3.73 – 3.45 (m, 2H), 3.09 – 2.77 (m, 2H), 2.09 (m, 1H), 1.69 – 1.44 (m, 2H), 1.44 – 1.24 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H), 0.84 (s, 9H), -0.01 (d, J = 3.5 Hz, 6H).

¹³C NMR (101 MHz, CDCl$_3$) δ 171.1, 156.8, 118.3, 61.4, 43.9, 36.4, 36.2, 26.3, 25.9, 18.3, 10.8, -5.3.

HRMS (ESI⁺): *m/z* calcd. for C$_{16}$H$_{31}$N$_2$OSi ([M+H⁺]) 295.22002, found 295.22001.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.8:0.2, 40 °C, 0.5 ml/min.), t$_R$ = 21.9 min (major), t$_R$ = 24.0 min (minor).

(R)-2-(2-ethyloctyl)-4,6-dimethoxy-1,3,5-triazine (14o)
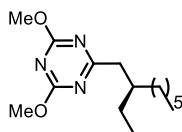
The reaction was performed using general procedure A, with 0.2 mmol **10o**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (R,S$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14o** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 96:04, v/v), [90% yield, 91% ee].
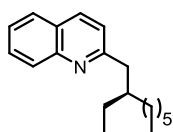
¹H NMR (400 MHz, CDCl$_3$) δ 4.00 (s, 6H), 2.63 (d, J = 7.1 Hz, 2H), 2.09 – 1.90 (m, 1H), 1.41 – 1.09 (m, 12H), 0.85 (m, 6H).

¹³C NMR (101 MHz, cdcl$_3$) δ 183.5, 172.3, 55.0, 42.9, 38.2, 33.0, 31.8, 29. 6, 26.4, 25.9, 22.6, 14.1, 10.7.

HRMS (ESI⁺): *m/z* calcd. for C$_{15}$H$_{28}$N$_3$O$_2$([M+H⁺]) 282.21760, found 282.21738.

CSP-HPLC: (242 nm, Chiralcel AD-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), t$_R$ = 12.1 min (major), t$_R$ = 13.2 min (minor).

(R)-2-(2-ethyloctyl)quinoline (14p)

The reaction was performed using general procedure A, with 0.1 mmol **10p**, BF$_3$·OEt$_2$ (0.15 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.15 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.005 mmol, 5 mol%),

ligand (*R*,*S*$_p$)-**L1** (0.006 mmol, 6 mol%) in 1mL Et$_2$O. Product **14p** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 97:03, v/v), [84% yield, 99% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 8.02 (dd, *J* = 8.5, 3.6 Hz, 2H), 7.73 (d, *J* = 1.4 Hz, 1H), 7.65 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 2.88 (d, *J* = 7.3 Hz, 2H), 2.03 – 1.81 (m, 1H), 1.42 – 1.09 (m, 12H), 1.01 – 0.73 (m, 6H).

¹³C NMR (101 MHz, cdcl$_3$) δ 162.6, 147.9, 135.8, 129.2, 128.9, 127.4, 126.6, 125.5, 121.9, 43.7, 40.0, 32.8, 31.8, 29.6, 26.5, 25.8, 22.6, 14.1, 10.7.

HRMS (ESI⁺): *m/z* calcd. for C$_{19}$H$_{28}$N([M+H⁺]) 270.22163, found 270.22156.

CSP-HPLC: (221 nm, Chiralcel OD-H, n-heptane/iPrOH = 99:1, 40 °C, 0.5 ml/min.), t$_R$ = 18.9 min (major), t$_R$ = 19.9 min (minor).

(*S*)-2-(2-phenyloctyl)benzoxazole (15a)
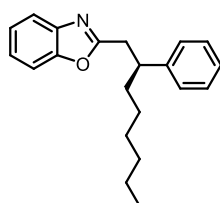
The reaction was performed using general procedure A, with 0.2 mmol **10a**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), *n*-HexMgBr (2M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **15a** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 95:05 → 90:10, v/v), [78% yield, 96% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 7.72 – 7.56 (m, 1H), 7.50 – 7.38 (m, 1H), 7.36 – 7.12 (m, 7H), 3.43 – 3.08 (m, 3H), 1.81 – 1.62 (m, 2H), 1.40 – 1.03 (m, 8H), 0.82 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (101 MHz, CDCl$_3$) δ 165.9, 150.7, 143.8, 141.3, 128.5, 127.4, 126.5, 124.4, 124.0, 119.6, 110.2, 44.0, 36.3, 35.9, 31.6, 29.2, 27.2, 22.6, 14.0.

HRMS (ESI⁺): *m/z* calcd. for C$_{21}$H$_{26}$N$_1$O$_1$ ([M+H⁺]) 308.20089, found 308.20101.

CSP-HPLC: (254 nm, Chiralcel AD-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), t$_R$ = 17.1 min (minor), t$_R$ = 17.6 min (major).

(S)-2-(6-methyl-2-phenylheptyl)benzoxazole (15b)
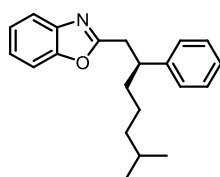
The reaction was performed using general procedure A, with 0.2 mmol **1a**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), *i*-HexMgBr (1.5M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **15b** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 98:02, v/v), [80% yield, 95% ee].

¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.58 (m, 1H), 7.53 – 7.39 (m, 1H), 7.36 – 7.13 (m, 7H), 3.40 – 3.11 (m, 3H), 1.83 – 1.63 (m, 2H), 1.51 – 1.35 (m, 1H), 1.32 – 0.99 (m, 4H), 0.78 (t, J = 6.5 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 165.9, 150.71, 143.8, 141.3, 128.5, 127.3, 126.5, 124.4, 124.0, 119.6, 110.2, 44.0, 38.7, 36.3, 36.1, 27.7, 25.1, 22.7, 22.4.

HRMS (ESI⁺): m/z calcd. for $C_{21}H_{26}N_1O_1$ ([M+H⁺]) 308.20089, found 308.20088.

CSP-HPLC: (254nm, Chiralcel AD-H, n-heptane/iPrOH = 99.8:0.2, 40 °C, 0.3 ml/min.), t_R = 31.7 min (minor), t_R = 32.2 min (major).

(*S*)-2-(5-methyl-2-phenylhexyl)benzoxazole (15c)
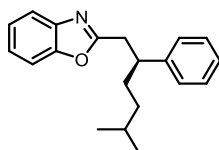
The reaction was performed using general procedure A, with 0.2 mmol **10a**, BF₃·OEt₂ (0.3 mmol, 1.5 equiv), *i*-PentMgBr (2M in Et₂O, 0.3 mmol, 1.5 equiv), CuBr·SMe₂ (0.01 mmol, 5 mol%), ligand (*R*,*S*ₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et₂O. Product **15c** was obtained as pale-yellow oil after column chromatography (SiO₂, pentane:EtOAc 95:05 → 90:10, v/v), [70% yield, 95% ee].

**¹H NMR** (400 MHz, CDCl₃) δ 7.70 – 7.59 (m, 1H), 7.52 – 7.39 (m, 1H), 7.36 – 7.11 (m, 7H), 3.41 – 3.06 (m, 3H), 1.90 – 1.65 (m, 2H), 1.48 (m, 1H), 1.21 – 0.94 (m, 2H), 0.80 (dd, J = 6.6, 4.0 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 165.9, 150.7, 143.8, 141.3, 128.5, 127.3, 126.5, 124.4, 124.0, 119.6, 110.2, 44.2, 36.4, 36.3, 33.7, 27.9, 22.7, 22.2.

HRMS (ESI⁺): m/z calcd. for $C_{20}H_{24}N_1O_1$ ([M+H⁺]) 294.18524, found 294.18531.

CSP-HPLC: (235 nm, Chiralcel AD-H, n-heptane/iPrOH = 99.8:0.2, 40 °C, 0.3 ml/min.), t_R = 34.6 min (minor), t_R = 35.5 min (major).

(*S*)-2-(4-methyl-2-phenylpentyl)benzoxazole (15d)
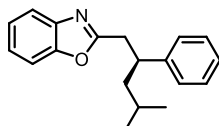
The reaction was performed using general procedure A, with 0.2 mmol **10a**, BF₃·OEt₂ (0.3 mmol, 1.5 equiv), i-ButMgBr (2M in Et₂O, 0.3 mmol, 1.5 equiv), CuBr·SMe₂ (0.01 mmol, 5 mol%), ligand (*R*,*S*ₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et₂O. Product **15d** was obtained as pale-yellow oil after column chromatography (SiO₂, pentane:EtOAc 95:05, v/v), [65% yield, 91% ee].

¹H NMR (400 MHz, CDCl₃) δ 7.69 – 7.59 (m, 1H), 7.44 (dt, J = 8.4, 3.2 Hz, 1H), 7.36 – 7.07 (m, 7H), 3.41 (m, 1H), 3.26 – 3.09 (m, 2H), 1.75 (ddd, J = 13.4, 10.4, 4.5 Hz, 1H), 1.49 (ddd, J = 13.6, 9.3, 4.9 Hz, 1H), 1.44 – 1.30 (m, 1H), 0.87 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H).

13C NMR (101 MHz, cdcl₃) δ 165.75 150.7, 143.7, 141.3, 128.5, 127.4, 126.5, 124.4, 124.0, 119.6, 110.2, 45.1, 41.9, 36.9, 25.3, 23.5, 21.5.

HRMS (ESI⁺): *m/z* calcd. for $C_{19}H_{22}N_1O_1$ ([M+H⁺]) 280.16959, found 280.16959.

CSP-HPLC: (234 nm, Chiralcel OD-H, n-heptane/iPrOH = 99:1, 40 °C, 0.5 ml/min.), t_R = 13.8 min (minor), t_R = 18.3 min (major).

(*R*)-2-(2-cyclopentyl-2-phenylethyl)benzoxazole (15e)
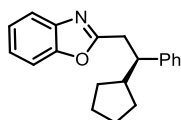
The reaction was performed using general procedure A, with 0.2 mmol **10a**, BF₃·OEt₂ (0.4 mmol, 2.0 equiv), cyclopentylMgBr (2M in Et₂O, 0.6 mmol, 3.0 equiv), CuBr·SMe₂ (0.01 mmol, 5 mol%), ligand (*R*,*S*ₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et₂O. Product **15e** was obtained as pale-yellow oil after column chromatography (SiO₂, pentane:EtOAc 99:01 → 92:08, v/v), [58% yield, 90% ee].

1H NMR (400 MHz, CDCl₃) δ 7.64 – 7.54 (m, 1H), 7.45 – 7.32 (m, 1H), 7.28 – 7.05 (m, 7H), 3.47 – 3.03 (m, 3H), 2.27 – 2.11 (m, 1H), 2.01 – 1.85 (m, 1H), 1.76 – 1.36 (m, 4H), 1.36 – 1.18 (m, 2H), 1.16 – 0.98 (m, 1H).

13C NMR (101 MHz, cdcl₃) δ 166.0, 150.6, 143.5, 141.3, 128.2, 127.7, 126.4, 124.2, 123.9, 119.5, 110.1, 49.9, 46.2, 35.1, 31.5, 31.4, 25.3, 24.8.

HRMS (ESI⁺): *m/z* calcd. for $C_{20}H_{22}N_1O_1$ ([M+H⁺]) 292.16959, found 292.16956.

CSP-HPLC: (242 nm, Chiralcel OD-H, n-heptane/iPrOH = 99:1, 40 °C, 0.5 ml/min.), t_R = 18.4 min (major), t_R = 35.2 min (minor).

(*S*)-2-(2-phenylhex-5-en-1-yl)benzoxazole (15f)
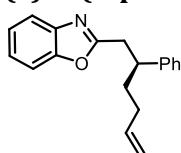
The reaction was performed using general procedure A, with 0.2 mmol **10a**, BF₃·OEt₂ (0.3 mmol, 1.5 equiv), but-3-en-1-ylMgBr(1.2M in Et₂O, 0.3 mmol, 1.5 equiv), CuBr·SMe₂ (0.01 mmol, 5 mol%), ligand (*R*,*S*ₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et₂O. Product **15f** was obtained as pale-yellow oil after column chromatography (SiO₂, pentane:EtOAc 95:05 → 80:20, v/v), [44% yield, 89% ee].

1H NMR (400 MHz, CDCl₃) δ 7.75 – 7.55 (m, 1H), 7.51 – 7.39 (m, 1H), 7.38 – 7.06 (m, 7H), 5.86 – 5.60 (m, 1H), 5.02 – 4.82 (m, 2H), 3.49 – 3.05 (m, 3H), 2.08 – 1.70 (m, 4H).

13C NMR (101 MHz, CDCl₃) δ 165.6, 150.7, 143.2, 141.2, 138.0, 128.6, 127.4, 126.7, 124.4, 124.0, 119.6, 114.9, 110.3, 43.4, 36.2, 34.9, 31.3.

HRMS (ESI⁺): *m/z* calcd. for $C_{19}H_{20}N_1O_1$ ([M+H⁺]) 278.15394, found 278.15399.

CSP-HPLC: (235 nm, Chiralcel AD-H, n-heptane/iPrOH = 99:1, 40 °C, 0.5 ml/min.), t_R = 19.2 min (minor), t_R = 22.5 min (major).

(S)-2-(2-phenylhept-6-en-1-yl)benzoxazole (15g)

The reaction was performed using general procedure A, with 0.2 mmol **10a**, BF₃·OEt₂ (0.3 mmol, 1.5 equiv), pent-4-en-1-ylMgBr(1.5M in Et₂O, 0.3 mmol, 1.5 equiv), CuBr·SMe₂ (0.01 mmol, 5 mol%), ligand (R,Sₚ)-**L1** (0.012 mmol, 6 mol%) in 2mL Et₂O. Product **15g** was obtained as pale-yellow oil after column chromatography (SiO₂, pentane:EtOAc 95:05 → 80:20, v/v), [57% yield, 93% ee].

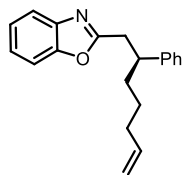**¹H NMR** (400 MHz, CDCl₃) δ 7.74 – 7.55 (m, 1H), 7.52 – 7.38 (m, 1H), 7.35 – 7.14 (m, 7H), 5.80 – 5.61 (m, 1H), 5.07 – 4.73 (m, 2H), 3.47 – 3.11 (m, 3H), 2.13 – 1.88 (m, 2H), 1.86 – 1.64 (m, 2H), 1.41 – 1.17 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 165.8, 150.7, 143.6, 141.3, 138.5, 128.5, 127.4, 126.6, 124.4, 124.0, 119.6, 114.5, 110.3, 43.9, 36.3, 35.3, 33.5, 26.5.

HRMS (ESI⁺): *m/z* calcd. for $C_{20}H_{22}N_1O_1$ ([M+H⁺]) 292.16959, found 292.16955.

CSP-HPLC: (234 nm, Chiralcel AD-H, n-heptane/iPrOH = 99:1, 40 °C, 0.5 ml/min.), t_R = 18.3 min (minor), t_R = 21.8 min (major).

(R)-2-(2-phenyl-4-(trimethylsilyl)butyl)benzoxazole (15h)
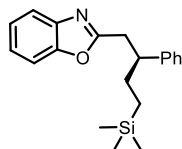
The reaction was performed with 0.15 mmol **10a**, BF₃·OEt₂ (0.3 mmol, 2.0 equiv), TMS(CH₂)₂MgBr (0.4 M in Et₂O, 0.45 mmol, 3.0 equiv), CuBr·SMe₂ (0.0075 mmol, 5 mol%), ligand (R,Sₚ)-**L1** (0.009 mmol, 6 mol%) in 1mL Et₂O. Product **15h** was obtained as pale-yellow oil after column chromatography (SiO₂, pentane:EtOAc 93:07, v/v), [74% yield, 95% ee].

¹H NMR (400 MHz, CDCl₃) δ 7.70 – 7.56 (m, 1H), 7.48 – 7.39 (m, 1H), 7.33 – 7.23 (m, 4H), 7.23 – 7.14 (m, 3H), 3.39 – 3.06 (m, 3H), 1.91 – 1.56 (m, 2H), 0.55 – 0.28 (m, 2H), -0.08 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 165.9, 150.7, 143.6, 141.3, 128.4, 127.5, 126.5, 124.3, 124.0, 119.5, 110.2, 47.0, 35.7, 30.3, 14.1, -1.8.

HRMS (ESI⁺): *m/z* calcd. for $C_{20}H_{26}N_1O_1Si$ ([M+H⁺]) 324.17782, found 324.17776.

CSP-HPLC: (235 nm, Chiralcel AD-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), t_R = 13.1 min (minor), t_R = 13.7 min (major).

(R)-(2-phenylpropyl)benzoxazole (15i)
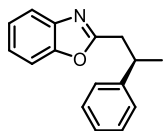
Reverse addition: Substrate **10h** (0.2 mmol in 1mL of Et$_2$O) was added over period of 1h (syringe pump) at -78 °C to a mixture of BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), PhMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R,S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 1mL Et$_2$O. Product **15i** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 99:01 → 95:05, v/v), [55% yield, 92% ee].

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 – 7.58 (m, 1H), 7.53 – 7.41 (m, 1H), 7.37 – 7.23 (m, 6H), 7.24 – 7.20 (m, 1H), 3.59 – 3.39 (m, 1H), 3.32 – 3.07 (m, 2H), 1.38 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 165.8, 150.7, 145.4, 141.2, 128.6, 126.6, 124.5, 124.1, 119.6, 110.3, 38.2, 37.3, 21.5.

HRMS (ESI$^+$): *m/z* calcd. for C$_{16}$H$_{16}$N$_1$O$_1$ ([M+H$^+$]) 238.12264, found 238.12253.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 99:1, 25 °C, 0.8 ml/min.), t$_R$ = 13.4 min (major), t$_R$ = 14.4 min (minor).

Note: Compared with reported data[14] (**HPLC conditions**: Chiralpak OD-H column, 99:1 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C; tr (major) = 10.1 min; tr (minor) = 11.8 min; 87% ee; ***R*-configuration**).

(R)-2-(2-butyloctyl)pyrimidine (15j)

The reaction was performed using general procedure A, with 0.2 mmol **10m**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), *n*-ButMgBr (3M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R,S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **15j** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 95:05, v/v), [94% yield, 99% ee].
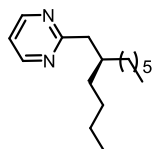
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.62 (d, *J* = 4.9 Hz, 2H), 7.06 (t, *J* = 4.9 Hz, 1H), 2.84 (d, *J* = 7.2 Hz, 2H), 2.10 – 1.93 (m, 1H), 1.36 – 1.06 (m, 16H), 0.91 – 0.75 (m, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 171.5, 156.7, 118.1, 44.4, 38.0, 33.6, 33.3, 31.8, 29.6, 28.7, 26.4, 22.9, 22.6, 14.03, 14.0.

HRMS (ESI$^+$): *m/z* calcd. for C$_{16}$H$_{29}$N$_2$ ([M+H$^+$]) 249.23253, found 249.23237.

CSP-HPLC: (250 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.8:0.2, 40 °C, 0.5 ml/min.), t$_R$ = 24.2 min (major).

(S)-2-(2-(4-methylpentyl)octyl)pyrimidine (15k)

The reaction was performed using general procedure A, with 0.1 mmol **10m**, BF$_3$·OEt$_2$ (0.15 mmol, 1.5 equiv), *i*-HexMgBr (1.5 M in Et$_2$O, 0.15 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.005 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.006 mmol, 6 mol%) in 1mL Et$_2$O. Product **15k** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 93:07, v/v), [89% yield, 99% ee].
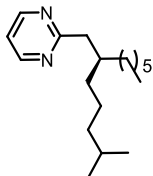
¹H NMR (400 MHz, CDCl$_3$) δ 8.65 (d, *J* = 4.9 Hz, 2H), 7.09 (t, *J* = 4.9 Hz, 1H), 2.87 (d, *J* = 7.2 Hz, 2H), 2.20 – 1.89 (m, 1H), 1.57 – 1.38 (m, 1H), 1.35 – 1.16 (m, 14H), 1.15 – 1.02 (m, 2H), 0.96 – 0.73 (m, 9H).

¹³C NMR (101 MHz, CDCl$_3$) δ 171.5, 156.7, 118.2, 44.5, 39.3, 38.1, 33.9, 33.7, 31.8, 29.6, 27.9, 26.4, 24.3, 22.6, 22.6, 22. 6, 14.1.

HRMS (ESI⁺): *m/z* calcd. for C$_{18}$H$_{33}$N$_2$ ([M+H⁺]) 277.26383, found 277.26371.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.7:0.3, 40 °C, 0.35 ml/min.), t$_R$ = 24.6 (minor), t$_R$ = 25.3 (major).

(R)-2-(2-isopentyloctyl)pyrimidine (15l)

The reaction was performed using general procedure A, with 0.2 mmol **10m**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), *i*-PentMgBr (2M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **15l** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 96:04, v/v), [91% yield, 99% ee].

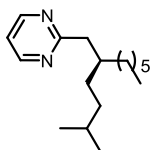**¹H NMR** (400 MHz, CDCl$_3$) δ 8.64 (d, *J* = 4.9 Hz, 2H), 7.08 (t, *J* = 4.9 Hz, 1H), 2.86 (d, *J* = 7.2 Hz, 2H), 2.12 – 1.87 (m, 1H), 1.52 – 1.36 (m, 1H), 1.36 – 1.05 (m, 14H), 0.94 – 0.71 (m, 9H).

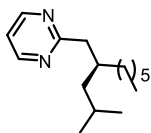**¹³C NMR** (101 MHz, CDCl$_3$) δ 171.5, 156.7, 118.2, 44.4, 38.2, 35.6, 33.6, 31.8, 31.2, 29.6, 28.2, 26.4, 22.6, 22.6, 22.5, 14.1.

HRMS (ESI⁺): *m/z* calcd. for C$_{17}$H$_{31}$N$_2$ ([M+H⁺]) 263.24818, found 263.24819.

CSP-HPLC: (250 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), 14.01 min (minor), t$_R$ = 14.7 min (major).

(S)-2-(2-isobutyloctyl)pyrimidine (15m)

The reaction was performed using general procedure A, with 0.2 mmol **10m**, BF$_3$·OEt$_2$ (0.3 mmol, 1.5 equiv), *i*-ButMgBr (2M in Et$_2$O, 0.3 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (R,S$_p$)-**L1** (0.012 mmol, 6 mol%) in mixture of Et$_2$O:DCM (1:0.5 mL). Product **15m** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 95:05, v/v), [78% yield, 98% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 8.68 (d, J = 4.9 Hz, 2H), 7.13 (t, J = 5.0 Hz, 1H), 2.98 – 2.78 (m, 2H), 2.13 (h, J = 6.4 Hz, 1H), 1.73 – 1.54 (m, J = 6.7 Hz, 1H), 1.47 – 1.16 (m, 10H), 1.16 – 1.02 (m, 2H), 0.99 – 0.75 (m, 9H).
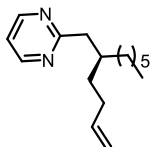
¹³C NMR (101 MHz, CDCl$_3$) δ 171.5, 156.7, 118.2, 44.8, 43.6, 35.8, 33.9, 31.8, 29.6, 26.2, 25.3, 23.0, 22.7, 22.6, 14.1.

HRMS (ESI⁺): *m/z* calcd. for C$_{16}$H$_{29}$N$_2$ ([M+H⁺]) 249.23253, found 249.23239.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), t$_R$ = 13.7 min (minor), t$_R$ = 14.2 min (major).

*_mixture of two enantiomer_*

(S)-2-(2-(but-3-en-1-yl)octyl)pyrimidine (15n)

The reaction was performed using general procedure A, with 0.1 mmol **10m**, BF$_3$·OEt$_2$ (0.2 mmol, 2.0 equiv), but-3-en-1-ylMgBr (1.2M in Et$_2$O), (1.2 M in Et$_2$O, 0.3 mmol, 3.0 equiv), CuBr·SMe$_2$ (0.005 mmol, 5 mol%), ligand (R,S$_p$)-**L1** (0.006 mmol, 6 mol%) in 1mL Et$_2$O. Product **15n** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 93:07, v/v), [90% yield, 99% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 8.65 (d, J = 4.9 Hz, 2H), 7.10 (t, J = 4.9 Hz, 1H), 5.76 (ddt, J = 16.9, 10.1, 6.6 Hz, 1H), 5.09 – 4.79 (m, 2H), 2.89 (dd, J = 7.2, 1.5 Hz, 2H), 2.21 – 1.92 (m, 3H), 1.48 – 1.15 (m, 12H), 0.85 (t, J = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl$_3$) δ 171.3, 156.8, 139.1, 118.3, 114.1, 44.3, 37.6, 33.5, 32.9, 31.8, 30.8, 29.6, 26.4, 22.6, 14.1.

HRMS (ESI⁺): *m/z* calcd. for C$_{16}$H$_{27}$N$_2$ ([M+H⁺]) 247.21688, found 247.21670.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.7:0.3, 40 °C, 0.35 ml/min.), t$_R$ = 28.9 (minor) t$_R$ = 29.8 (major).

(*S*)-2-(2-(pent-4-en-1-yl)octyl)pyrimidine (15o)

The reaction was performed using general procedure A, with 0.1 mmol **10m**, BF$_3$·OEt$_2$ (0.2 mmol, 2.0 equiv), pent-4-en-1-ylMgBr (1.5 M in Et$_2$O, 0.3 mmol, 3.0 equiv), CuBr·SMe$_2$ (0.005 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.006 mmol, 6 mol%) in 1mL Et$_2$O. Product **15o** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 93:07, v/v), [51% yield, 99% ee].
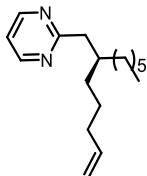
¹H NMR (400 MHz, CDCl$_3$) δ 8.66 (d, *J* = 4.9 Hz, 2H), 7.11 (t, *J* = 5.0 Hz, 1H), 5.77 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.06 – 4.82 (m, 2H), 2.88 (d, *J* = 7.2 Hz, 2H), 2.18 – 1.88 (m, 3H), 1.46 – 1.16 (m, 14H), 0.86 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl$_3$) δ 171.4, 156.8, 139.0, 118.2, 114.2, 44.4, 37.9, 34.0, 33.6, 33.1, 31.8, 29.6, 26.5, 25.8, 22.6, 14.1.

HRMS (ESI⁺): *m/z* calcd. for C$_{17}$H$_{29}$N$_2$ ([M+H⁺]) 261.23253, found 261.23229.

CSP-HPLC: (245 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.7:0.3, 40 °C, 0.35 ml/min.), t$_R$ = 30.2 (minor), t$_R$ = 30.6 (major).

(*R*)-2-(2-(2-(trimethylsilyl)ethyl)octyl)pyrimidine (15p)

The reaction was performed using general procedure A, with 0.1 mmol **10m**, BF$_3$·OEt$_2$ (0.2 mmol, 2.0 equiv), TMS(CH$_2$)$_2$MgBr (0.4 M in Et$_2$O, 0.3 mmol, 3.0 equiv), CuBr·SMe$_2$ (0.005 mmol, 5 mol%), ligand (*R*,*S*$_p$)-**L1** (0.006 mmol, 6 mol%) in 1mL Et$_2$O. Product **15p** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 93:07, v/v), [78% yield, 97% ee].
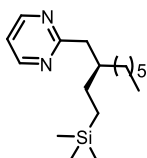
¹H NMR (400 MHz, CDCl$_3$) δ 8.65 (d, *J* = 4.9 Hz, 2H), 7.09 (t, *J* = 4.9 Hz, 1H), 2.99 – 2.78 (m, 2H), 2.09 – 1.90 (m, 1H), 1.38 – 1.12 (m, 12H), 0.85 (t, *J* = 6.8 Hz, 3H), 0.59 – 0.33 (m, 2H), -0.08 (s, 9H).
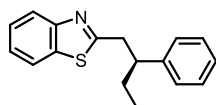
¹³C NMR (101 MHz, CDCl$_3$) δ 171.6, 156.7, 118.2, 43.8, 40.5, 33.0, 31.8, 29.6, 27.0, 26.5, 22.6, 14.1, 12.3, -1.9.

HRMS (ESI⁺): *m/z* calcd. for C$_{17}$H$_{33}$N$_2$Si$_1$ ([M+H⁺]) 293.24075, found 293.24074.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), t$_R$ = 12.2 min (minor), t$_R$ = 13.6min (major).

2.4.5 Catalytic Asymmetric Addition of EtMgBr to (*E*)-1i and (*Z*)-1i

(*S*)-2-(2-phenylbutyl)benzothiazole (14i)

The reaction was performed using general procedure A, with 0.2 mmol **(E)-10i**, BF$_3$·OEt$_2$ (0.44 mmol, 2.2 equiv), EtMgBr (3M in Et$_2$O, 0.6 mmol, 3.0 equiv), CuBr·SMe$_2$ (0.01 mmol, 5 mol%), ligand (*R,S*$_p$)-**L1** (0.012 mmol, 6 mol%) in 2mL Et$_2$O. Product **14i** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 99:01 → 97:03, v/v), [88% yield, 86% ee].

¹H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.43 (m, 1H), 7.34 – 7.27 (m, 3H), 7.25 – 7.17 (m, 3H), 3.55 – 3.31 (m, 2H), 3.12 (m, 1H), 2.00 – 1.62 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl$_3$) δ 170.5, 153.0, 143.5, 135.2, 128.5, 127.8, 126.6, 125.8, 124.6, 122.5, 121.4, 48.1, 41.3, 29.2, 11.9.

HRMS (ESI⁺): *m/z* calcd. for C$_{17}$H$_{18}$NS ([M+H⁺]) 268.11545, found 268.11541.

CSP-HPLC: (254 nm, Chiralcel OD-H, n-heptane/iPrOH = 99:1, 40 °C, 0.5 ml/min.), t$_R$ = 14.5 min (major), t$_R$ = 18.2 min (minor).

(*R*)-2-(2-phenylbutyl)benzothiazole (14i)
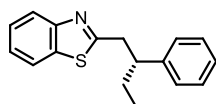
The reaction was performed using general procedure A, with 0.1 mmol **(Z)-10i**, BF$_3$·OEt$_2$ (0.15 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.15 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.005 mmol, 5 mol%), ligand (*R,S*$_p$)-**L1** (0.006 mmol, 6 mol%) in 1mL Et$_2$O. Product (*R*)-**14i** was obtained as pale-yellow oil after column chromatography (SiO$_2$, pentane:EtOAc 97:03, v/v), [88% yield, 40% ee]

2.4.6 Controlled Experiments

a) Reaction with 1 mol% of catalyst: Reaction was performed using general procedure A, with 0.5 mmol **10m**, BF$_3$·OEt$_2$ (0.75 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.75 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.005 mmol, 1 mol%), ligand (*R,S*$_p$)-**L1** (0.006 mmol, 1.2 mol%) in 1mL Et$_2$O, product **14m** was isolated as above, with [90% yield, 99% ee].

b) Preparative scale reaction: Reaction was performed using general procedure A, with 1mmol of **10m**, BF$_3$·OEt$_2$ (1.5 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 1.5 mmol, 1.5 equiv), CuBr·SMe$_2$ (0.05 mmol, 5 mol%), ligand (*R,S*$_p$)-**L1** (0.06 mmol, 6 mol%) in 8 mL Et$_2$O, product **14m** was isolated as above, with [84% yield, 99% ee]. Cu-complex was isolated as orange solid after column chromatography (SiO$_2$, pentane:EtOAc 80:20 v/v), [0.035 mmol, 75% yield].

c) Reaction with recovered catalyst: Reaction was performed using general procedure A, with 0.1 mmol of **10m**, BF$_3$·OEt$_2$ (0.15 mmol, 1.5 equiv), EtMgBr (3M in Et$_2$O, 0.15 mmol, 1.5 equiv), *Cu-complex recovered from preparative scale* (0.005 mmol, 5 mol%), in 1 mL Et$_2$O, product **14m** was isolated as above, with [87% yield, 99% ee].

2.4.7 *(E)/(Z)* Photoisomerization Experiments

A solution of (*E*)-2-styrylbenzothiazole (**10i**) in 6 screw cap glass vials (each vial contain 25mg in 2.5 mL CH$_2$Cl$_2$) was irradiated with 365-nm light [Spectroline model ENC-280C/FE lamp] for 5h (NMR monitoring). The solvent from resulting yellow solution was evaporated in vacuo to provide not separable mixture of (*E*) and (*Z*)-2-styrylbenzothiazole with 10:90 ratio.

2.4.8 (*E*)/(*Z*) Isomerization Experiments of (*Z*)-10i (E/Z=10:90)

Four different sets of experiments were carried out as below.

a) With (*Z*)-10i and BF$_3$·OEt$_2$

In a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar was dissolved **(*Z*)-10i** (20mg, 0.084 mmol) in Et$_2$O (1 mL). Reaction mixture was cooled to -78 °C and added BF$_3$·OEt$_2$ (18 mg/ 15.6 µL, 0.126 mmol, 1.5 equiv). After 15 h at -78 °C reaction mixture was quenched by adding MeOH (1 mL) followed by saturated aqueous NH$_4$Cl solution and warmed to RT. Reaction mixture was extracted with CH$_2$Cl$_2$ (2 × 10mL). Combined organic phases were dried over MgSO$_4$, filtered and solvents were evaporated on rotary evaporator to obtained crude. The (*E*)/(*Z*) ratio was determined by ^{1}H NMR on the isolated crude.

b) With (*Z*)-10i and MeMgBr

In a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar was dissolved **(*Z*)-10i** (20mg, 0.084 mmol) in Et$_2$O (1 mL). Reaction mixture was cooled to -78 °C and added MeMgBr (3M in Et$_2$O, 42 µL, 0.126 mmol, 1.5 equiv). After 15 h reaction mixture was quenched and crude was isolated, and The (*E*)/(*Z*) ratio was determined as above.

c) With (*Z*)-10i, BF$_3$·OEt$_2$ and MeMgBr

In a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar was dissolved **(*Z*)-10i** (20mg, 0.084 mmol) in Et$_2$O (1 mL). Reaction mixture was cooled to -78 °C and added BF$_3$·OEt$_2$ (18 mg/ 15.6 µL, 0.126 mmol, 1.5 equiv), followed by MeMgBr (3M in Et$_2$O, 42 µL, 0.126 mmol, 1.5 equiv). After 15 h reaction mixture was quenched and crude was isolated, and The (*E*)/(*Z*) ratio was determined as above.

d) With CuBr·SMe$_2$ / (*R*,*S*$_p$)-L1, (*Z*)-1i, BF3·OEt2 and MeMgBr

In a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar was dissolved the CuBr·SMe$_2$ (8.63mg, 0.042 mmol, 1 equiv), and ligand (*R*,*S*$_p$)-**L1** (27.52 mg, 0.046 mmol, 1.1 equiv) were dissolved in Et$_2$O (1mL) and stirred under nitrogen atmosphere for 15 min. The substrate (10 mg, 0.042 mmol, 1 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C and BF$_3$·OEt$_2$ (8 µL, 0.063 mmol, 1.5 equiv) was added followed by MeMgX (3M in Et$_2$O, 21 µL, 0.063 mmol, 1.5 equiv). After stirring for 15 h at -78 ºC reaction was quenched and crude was isolated, and The (*E*)/(*Z*) ratio was determined as above.

2.4.9 Determination of Absolute Configuration

The absolute configuration was determined by comparison HPLC data for compound **15i** with reported data[14] (HPLC conditions: Chiralpak OD-H column, 99:1 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C; tr (major) = 10.1 min; tr (minor) = 11.8 min; 87% ee; ***R*-configuration**). The absolute configurations of other compounds were assigned by analogy.

2.5 Bibliography

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