Chapter 5

On the Cu Catalysed Conjugate Addition of Grignard Reagent to Alkenyl Pyridine Derivatives: a Mechanistic Study

In this chapter, the mechanistic studies of the Cu catalysed conjugate addition of Grignard reagents to alkenyl pyridine derivatives discussed in chapter 4 is presented. Extensive studies on different Lewis acids have been carried out in order to acquire a deeper understanding on their role(s) in the transformation. Furthermore, a series of experiments and NMR studies led to the identification of important reaction intermediates. Finally, a tentative catalytic cycle for this transformation has been proposed.

Part of this chapter has been published:


5.1 Introduction

Copper catalysed asymmetric conjugate addition (ACA) of organometallic nucleophiles to electron-poor olefins is one of the most exploited tools for the construction of new C-C bonds in organic synthesis. Despite its popularity, for many years the scientific community had a vague idea of the events taking place in the catalytic cycle. Extended mechanistic studies have been carried out on the addition of stoichiometric amount of organocuprates to enones and enoates. Several mechanisms have been proposed for this transformation and all of them have suggested π-complex formation between the Cu(I) species and the double bond of the Michael acceptor as the first step (Scheme 1). This species can evolve in the final product either via formation of Cu(III) species (Scheme 1a), derived from formal oxidative addition, or via a carbocupration intermediate (Scheme 1b).

Existence of these intermediates was supported primarily by theoretical studies. The first attempts to observe them experimentally, have been carried out by Ullenius and co-workers. Major indicator of the formation of π-complex between lithium dimethyl cuprate (Gilman reagent) and different enoates, was a shift towards higher field of the $sp^2$ carbons of the double bond recorded in the $^{13}$C-NMR. Years later Ogle et al. observed similar results using Rapid Injection NMR spectroscopy (RI-NMR) at low temperature using Gilman reagents and different Michael acceptors such as enone, enoates and α,β-unsaturated nitriles. If clear evidences of formation of complex were found, the debate on which pathway was more likely to take place after the first step was still open and remained that way for long time. The groundbreaking work of Ogle and co-workers finally shone light on the problem. Thanks to advanced RI-NMR techniques, they were able to characterize the elusive Cu(III) intermediate (Scheme 2). Key role in this breakthrough was displayed by the stabilizing effect of the substituents on the metallic centre in complex 7.

![Scheme 1: Proposed mechanism for Cu catalysed conjugate addition.](image)

![Scheme 2: Formation of Cu(III) intermediate 7.](image)
These experimental proofs indicate the pathway depicted in Scheme 1a as the most probable one, even though there are some cases in which the carbocupration route seems predominant. Despite the amount of data collected on the stoichiometric version of this transformation, only a few studies have been carried out in presence of chiral ligands and/or in catalytic regime. Harutyunyan et al. conducted detailed studies on the formation of the Cu(I)-diphosphine complexes using different spectroscopic techniques as well as X-ray and electrochemical analysis. Based on the data obtained, they conclude that copper halide salts, in presence of diphosphine ligands, form dinuclear Cu-complex in which the halide counterion is bridging between the metallic centres. Reaction of the abovementioned dinuclear Cu-complex with a molecule of Grignard reagent yields a mixed Cu/Mg complex that is the catalytically active species (Scheme 3).

Scheme 3: Formation of copper complexes in presence of diphosphine ligands and Gignard reagents.

Other studies on the structure of Cu/phosphine ligand complexes and their transmetallation in presence of organozinc reagents have been carried out by the group of Gschwind using 2D-NMR spectroscopy. Detection and characterisation of the Cu(III) species in catalytic conditions in presence of ligand have not been yet reported.

In light of these results, assuming that the mechanism of copper catalysed reactions might follow the stoichiometric CA pathway, a tentative catalytic cycle for addition of Grignard reagents was proposed (Scheme 4).

Scheme 4: Proposed catalytic cycle for Cu catalysed ACA to enones and enoates.

Copper bromide/diphosphine ligand binuclear complex 8 reacts with one molecule of Grignard reagent in order to form the transmetallated active species 9. This species forms π-complex 11 with Michael acceptor 10 in a reversible way. Complex 11 then undergoes oxidative addition evolving in intermediate 12 that upon reductive elimination affords product 13 leading to the
initial copper complex. Reaction of the latter with a molecule of RMgX restores the active species closing the catalytic cycle.

Identification of the Rate Determining Step (RDS) for CA is another controversial topic. In their work on the 1,4 addition of zinc reagents to cyclohexenone catalysed by Cu/sulphonamide system, Noyori, Kitamura and co-workers have proposed a concerted mechanism with the alkyl group transfer as RDS based on kinetic studies and $^{12}\text{C}/^{13}\text{C}$ isotope effect. Similar results were obtained by Schrader and co-workers using Cu(I) salts in combination with phosphorus ligands. To a total different direction pointed the studies of Gennari and co-workers. Asymmetric conjugate addition of diethylzinc to cyclohexenone promoted by Cu/Schiff base ligand revealed the oxidative addition of the transmetallated copper complex as the RDS.

Our catalytic system employs reagents and reaction conditions similar to those used for CAs to carbonyl based Michael acceptors, but contrary to these, alkenyl pyridines are unreactive substrates towards organometallics in absence of LA, even at non-cryogenic conditions. Moreover, if the addition follows the same pathway, the aromaticity of the pyridines will be altered in several intermediate species. The necessity of LA to accomplish ACA to alkenyl pyridines adds another level of mechanistic complexity. To gain insight into the reaction mechanism involved in the ACA of Grignard reagent to alkenyl pyridines developed in our group, a series of experiments and NMR studies were carried out and will be discussed in the following paragraphs.

5.2 Results and Discussion

The experimental data discussed in Chapter 4 demonstrate that TMSOTf is the best LA for 4-alkenyl pyridines, while BF$_3$-OEt$_2$ is the most suitable LA for 2-alkenyl pyridines. Additionally, it was found that no reaction occurs with non-activated 2-alkenyl pyridines in presence of either LAs. Only after introducing an electron withdrawing group (EWG) in the pyridine ring, CAs are possible using BF$_3$-OEt$_2$. In contrast, in presence of TMSOTf as LA, full conversion to side products deriving from the attack to the pyridine ring occurs. On the other hand, non-activated 4-alkenyl pyridines can only be converted to CA products using TMSOTf. This trend was further confirmed by the results obtained upon subjecting compound 14, bearing 4- and 2-alkenyl pyridine moieties, to the standard reaction conditions (Scheme 5). In presence of TMSOTf, compound 14 afforded exclusively the conjugate addition product 15, while employing BF$_3$-OEt$_2$ as LA resulted in a mixture of both compounds 15 and 16 in a ratio of 10:1 respectively (Scheme 5).
Scheme 5: Ethylation of substrate 14 in presence of TMSOTf and BF₃·OEt₂.

This experiment indicate unambiguously that 4-alkenyl pyridines are intrinsically more reactive towards CA than their 2-alkenyl analogues. Further information on the reactivity of pyridine substrates and the effect of LAs were obtained from ¹H-NMR spectroscopic studies. The interactions between various reagents (LAs and EtMgBr) and substrate 17 were investigated by performing NMR measurement in deuterated dichloromethane (CD₂Cl₂) at -60 °C (Figure 1).

Figure 1: Effect of different LA on compound 17. Reaction condition: a) 17 0.1mmol, CD₂Cl₂ 1ml, -60 °C; b) 17 0.1mmol, TMSOTf 2.0 equiv, CD₂Cl₂ 1ml, -60 °C; c) 17 0.1mmol, BF₃·OEt₂ 2.0 equiv, CD₂Cl₂ 1ml, -60 °C; d) 17 0.1mmol, TMSCl 2.0 equiv, CD₂Cl₂ 1ml, -60 °C; e) 17 0.1mmol, EtMgBr 2.0 equiv, CD₂Cl₂ 1ml, -60 °C.
In all the experiments, a substantial shift of the signals belonging to the pyridine ring and the alkenyl moiety was observed. In particular we followed the downfield shifts of the olefinic protons which are indicative of a reduction of the electron density around carbon a and b shown in Figure 1. The most pronounced shift was recorded when TMSOTf was employed (Figure 1b) while EtMgBr showed the smallest shift (Figure 1d). Intermediate results were observed for BF$_3$·OEt$_2$ and TMSCl (Figures 1c and 1d respectively). Based on the shifts for substrate 17 upon mixing with either TMSOTf, BF$_3$·OEt$_2$, TMSCl and EtMgBr we can rank these reagents in terms of their activating Lewis acidic strength as: TMSOTf > BF$_3$·OEt$_2$ > TMSCl > EtMgBr. Similar trend was observed for substrate 18 (Figure 2).

**Figure 2**: Effect of different LA on compound 18. Reaction condition: a) 18 0.1mmol, CD$_2$Cl$_2$ 1ml, -60 °C; b) 18 0.1mmol, BF$_3$·OEt$_2$ 1.5 equiv, CD$_2$Cl$_2$ 1ml, -60 °C; c) 18 0.1mmol, EtMgBr 2.0 equiv, CD$_2$Cl$_2$ 1ml, -60 °C.

To study the effect of strength and bulkiness of LAs on the CA of EtMgBr to substrate 17, two sets of experiments were carried out either in presence or absence of the Cu-L1 complex (Table 1).
### Table 1: Evaluation of strength, counterion and steric effects of different LAs in the CA to substrate 17.

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<th>Entry</th>
<th>LA</th>
<th>T (°C)</th>
<th>Cu/L1 (mol%)</th>
<th>Conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>10</td>
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<sup>a</sup> Determined by ¹H NMR; <sup>b</sup> Determined by chiral HPLC; Reaction conditions: 17 (0.1mmol), CuBr·SMe₂ (10 mol%), L1 (12 mol%), LA (3 equiv), EtMgBr (3 equiv), DCM (1ml).

As already mentioned, in either case no conversion occurs when using BF₃·OEt₂ as LA (Table 1, entries 1 and 5) whereas full conversion is observed for TMSOTf (Table 1, entries 4 and 7). The enantioselectivity of 93% obtained with TMSOTf (Table 1, entry 7) is particularly remarkable since the LA-promoted background reaction in the absence of a copper catalyst is complete at -78 °C in 4 hours (Table 1, entry 4). A closer look at the LA strength by varying the counterion of the silicon based LA confirmed that as expected, with the very weak TMSCl and somewhat stronger TMSBr no conversion was observed after 15h without catalyst (Table 1, entries 3 and 9). Remarkably though, in the presence of the Cu-catalyst full conversion to the CA product was observed with TMSBr (Table 1, entry 10) and 60% conversion with TMSCl (Table 1, entry 8) and in both cases only one enantiomer was found. These results were unexpected, especially for the rather weak TMSCl. The effect of the bulkiness of the LA was investigated by testing a number of different steric variations of silyl triflates (Table 1, entries 11-14). To our surprise, an increase of steric bulk at the silicon atom resulted in decreased enantioselectivity: moving to TMS- to triethylsilyl (TES-), tert-butyldimethylsilyl (TBS-), and finally to tert-butyldiphenylsilyl (TBDPS-) substituted triflates, the ee dropped from 93 to 62% (Table 1, entries 7, 11-14). From these experiments, it is not clear whether these differences in enantioselectivity are caused by steric bulk alone. The 40% conversion observed with TBDPSOTf without catalyst (Table 1, entry 14) shows that background reaction is relevant, and thus that differences in the relative rates of the racemic non-catalysed with respect to the enantioselective Cu catalysed CA reactions might also affect the enantioselectivity. Interestingly, in contrast to the result with TMSCl, carrying out the
Cu catalysed reaction using TBS- and TBDPS-chlorides at both -78 °C and 0 °C did not give any substrates conversion (Table 1, entries 15, 16). However, after screening of various LAs conditions we found a set of experiments that settles this matter (Table 1, entries 17-19). At 0 °C the catalysed reaction with TMSCl gives an ee of 91% (Table 1, entry 19), while the same reaction with TESCl yields an ee of 82% (Table 1, entry 17). Importantly, without the catalyst no conversion is observed with TESCl, which unambiguously shows that the decreased enantioselectivity is not due to a background reaction and thus must be due to the larger bulk of the LA. All together, these results prove that the bulkiness of the LAs affects both the enantioselectivity and the reactivity adversely and thus imply that the LAs are involved in both rate- and stereodetermining steps.

Our investigation continued by studying the influence of the geometry of the double bond, another important parameter for both reactivity and selectivity in addition reactions. Furthermore, when starting from less stable (Z)-alkenes, isomerization to the (E)- stereoisomer might occur during the course of the reaction, thus affecting the overall reaction outcome while providing useful hints to understand the mechanism of the reaction. Therefore, the influence of the alkene [(Z)/(E)] geometry on the enantioselective CA of EtMgBr to compounds 17 and 18, in presence of TMSOTf and BF3·OEt2 respectively, was studied.

When subjecting compounds (Z)-17 and (Z)-18 to the optimised reaction conditions, the enantioselectivities obtained in both reactions were lower than with (E)-17 and (E)-18 (Table 2, entry 1 vs entry 2, entry 8 vs entry 9). Although the reduction in ee in the catalytic reaction could be related to the partial isomerization of the corresponding (Z)-substrate double bond during the reaction, the subsequent additional control experiments proved that the decreased enantioselectivity is intrinsic to the (Z)-geometry of the substrate and not due to (Z)-(E) isomerization (Table 2, entries 3-7).
Table 2: Isomerization experiments

<table>
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<th>Entry</th>
<th>Alkene</th>
<th>LA</th>
<th>Cu/L1 (%)</th>
<th>RMgBr</th>
<th>Conv. (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>(Z):(E)&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;[c]&lt;/sup&gt;</th>
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All the isomerization studies were carried out at -78 °C in DCM for 15h unless mentioned otherwise. [a] Conversions were determined by 1H NMR; [b] Ratio (Z):(E) was determined by 1H NMR; [c] Determined by chiral HPLC; [d] Similar results were obtained quenching the reaction after 30 minutes;[e] Reaction quenched after 1h.

Compound (Z)-18 was subjected to a similar set of experiments in which BF<sub>3</sub>-EtO was used as LA. The results obtained confirmed the trend found with compound (Z)-17 (Table 2, entries 9-13). This is at odds with our previous findings for the Cu catalysed CA to other N-containing alkenyl heteroarenes<sup>[15]</sup>, where we clearly observed isomerization of alkenyl benzothiazole caused by all reaction components in combination, thus supporting Cu(I)/Cu(III) redox chemistry with reversible formation of π- to σ- Cu-complexes responsible for substrates isomerization.<sup>[15]</sup> The lack of Cu mediated isomerization in the present case does not rule out this mechanism, but might be suggestive of other possibilities.

To complete our study, we wanted to elucidate the structure of the initial product of these CA reactions before the reaction mixture is quenched. In particular, the question is whether a non-aromatic enol-like structure is formed and if so, whether it is a Mg-enolate or a LA-derived enolate (silyl enol ether for TMSOTf and boron enolate for BF<sub>3</sub>-OEt<sub>2</sub>). In the case of Cu catalysed CA of EtMgBr to compound 17 in the presence of TMSOTf, we only observed the formation of silyl-enolate (Figures 3b and 4).
Figure 3: a) NMR spectrum of compound 17; b) NMR spectrum of enolate 21 before the reaction mixture is quenched; c) NMR spectrum of compound 19.

Figure 4: NOESY effect of proton H and H (6.1 ppm) with the trimethylsilyl moiety (0.2 ppm) in enolate 21.

Unfortunately, in the case of CA to compound 18 using BF₃·OEt₂, efforts to characterize the product structure before quenching of the reaction were hampered by severely broad signals observed in ¹H-NMR.
The presence of LA is a necessary condition to promote the enantioselective CA to alkenyl pyrimidines. The fact that LA promotes not only Cu catalysed but also in several instance non-catalytic background reaction, makes it difficult to elucidate its role precisely. LA additives have been known to accelerate CA of organocuprates to various α,β-unsaturated carbonyl derivatives. However, strong LAs, such as BF$_3$·OEt$_2$, were only used in combination with stoichiometric amounts of organocupper reagent (Yamamoto reagent) to avoid compatibility problems commonly encountered between Grignard reagents and LAs. In contrast, for Cu catalysis, as well as for stoichiometric reactions, the use of TMSCl, which is more a silylating agent than a LA, became common practice in CA. In our case, we use catalytic amounts of chiral copper complex in combination with strong LAs, which do not only activate the pyridine substrate but also interfere with the CA by reacting with the Grignard reagent or decomposing the chiral Cu-complex catalyst. As a result, the outcome of the reaction depends critically on the relative rates of the desired catalysed vs the undesired background pathway, as well as on these competing reactions. The proposed reaction pathway, based on experimental and spectroscopic data and taking into account the previous proposal on Cu catalysed CA, is presented in Scheme 6. We expect that the first step in the catalytic cycle is the formation of the catalytically active complex 9 upon transmetallation of precatlyst 8 with Grignard reagent in a similar manner as has been proposed for Cu catalysed CA to carbonyl based Michael acceptors employing similar solvent and diphosphine ligands (Scheme 4). The first intermediate (23) in the proposed cycle is formed via π-complexation between activated alkenyl pyridine 22 and complex 9. This is then followed by the formation of σ-complex intermediate 24. We anticipated the activated alkenyl pyridine 22 to be an LA-pyridine complex, the formation of which was indeed observed by $^1$H-NMR spectroscopy when using either TMSOTf, TMSCl or BF$_3$·OEt$_2$ (Figure 1). Interestingly, although theoretically TMSCl is the weakest silicon based LA, especially in comparison with BF$_3$·OEt$_2$, it nevertheless is able to catalyse the reaction with non-activated substrate 17, in contrast to BF$_3$·OEt$_2$. These findings indicates that the role of the LA is not limited to the initial Lewis acidic substrate activation. Rather, it is also involved in the acceleration of the reaction via silylation of the reaction intermediate, leading to the formation of more stable non aromatic intermediate 24 and silyl aza-enolate 21 (Scheme 6).
Another aspect of the critical function of the LA in the catalytic cycle is evident from the observation that its bulkiness plays an important role in defining the enantioselectivity (Table 1). The decrease in enantioselectivity from 91% to 82% when moving from TMSCl to TESCl can only be attributed to the bulkiness of the LA and not to its capability of promoting non-catalysed CA, since there is no background TESCl promoted reaction in the absence of Cu catalyst (Table 1, entries 8, 17-19). The origin of this effect in our system is unclear, as well as which are the rate- and enantiodetermining steps. The mechanistic pathway for Cu catalysed CA, as well the origin of the accelerations observed for reactions with TMSCl, have been the subject of considerable debate. However, so far the mechanism has been studied only for stochiometric reactions with organocopper reagents. The current view is that the oxidative addition step is reversible and the following reductive elimination is the rate limiting step. This is supported by \((Z)-(E)\) isomerization observed in CA of organocopper reagents using \((Z)\)-enones and \((Z)\)-enoates, as well as by kinetic isotope effect studies. With respect to the role of TMSCl, several hypothesis were raised, namely silylation of π-complex to form silyl enol ether of σ-complex, by Corey,\(^{17a,17b}\) LA activation of the enone substrates, by Kuwajima,\(^{17d}\) and stabilization of the σ-complex by the chloride of TMSCl, by Snyder and Bertz.\(^{17e}\) Kinetic isotope experiments by Singleton and co-workers\(^{17f}\) resolved this question for the systems studied, with the data consistent with a rate limiting silylation of an intermediate π-complex. This also explains the lack of \((Z)-(E)\) isomerization observed in presence of TMSCl, which is then due to the rate limiting step occurring earlier than in the system without TMSCl. Our experiments differ from these mechanistic studies in two aspects, namely the fact that we use a catalytic system and a more Lewis basic substrate. In this case, any LA we use is involved in the catalytic cycle from the...
start of the reaction, through complexation with the pyridine substrate. In principle, steps 1-3 (Scheme 6) all lead to the formation of a chiral intermediate, and the fact that the bulkiness of the LA influences the ee indicates its involvement in the stereo-determining step. Similarly, any of these steps can be rate limiting, and the lack of isomerization caused by LA/Cu/RMgBr does not distinguish between the steps. The evidences collected so far do not allow the definition of the RDS of the reaction, but some considerations can be drawn. Looking at the proposed mechanism (Scheme 6), step 2 and step 3 are those who will probably benefit more from the LA complexation, either because of the increased electrophilicity of the β-carbon in 22 or the stabilization of non-aromatic intermediate 21. Thus, it is reasonable to assume that the rate of those steps will be affected upon LA addition the most. On the other hand, step 1 is likely to benefit less from the silylation of 17. Moreover, since the bulkiness of the LA is interfering with the catalyst in the stereodetermining step, it is plausible that it will interfere as well in the formation of π-complex 23 hampering its formation. Of course, to support this or any other hypothesis on the identification of the RDS of the reaction extensive kinetic studies are required.

5.3 Conclusion

Experiments described in this chapter were aimed at gaining some mechanistic understanding for this transformation. With the data obtained complete unravelling of the catalytic cycle is not possible but some interesting conclusion can be made and used for further studies. From these studies, it has emerged that the LA is not only responsible for the activation of the substrates but also involved in the stereo-determining step, manifested by clear dependence of the asymmetric induction on the steric bulk of the Lewis acid. It also appears that the stabilization of reaction intermediate granted by LA complexation has a stronger influence on the reactivity than its ability to withdraw electron density from the conjugate double bond, as demonstrated by the results obtained when using BF$_3$:OEt$_2$ and TMSCl (Table 1, entry 5 vs 7). Moreover, a non-aromatic enolate-type structure has been identified in the reaction mixture before it was quenched, suggesting that non-aromatic Cu(III) intermediate could be also a viable intermediate
5.4 Experimental Section

5.4.1 General Information

All reactions using oxygen- and/or moisture-sensitive materials were carried out with anhydrous solvents (vide infra) under a nitrogen atmosphere using oven dried glassware and standard Schlenk techniques. Reactions were monitored by $^1$H NMR. Purification of the products, when necessary, was performed by flash-column chromatography using Merck 60 Å 230-400 mesh silica gel. NMR data was collected on Bruker Avance NEO 600 ($^1$H at 600.0 MHz; $^{13}$C at 150.87 MHz), equipped with a Prodigy Cryo-probe, Varian Inova 500 ($^1$H at 500.0 MHz; $^{13}$C at 125.72 MHz, $^{19}$F at 470.37 MHz), equipped with an Indirect Detection probe and Varian VXR400 ($^1$H at 400.0 MHz; $^{13}$C at 100.58 MHz, $^{19}$F at 376.29, $^{31}$P at 161.94 MHz), equipped with a 5 mm z-gradient broadband probe. Chemical shifts are reported in parts per million (ppm) relative to residual solvent peak (CDCl$_3$, $^1$H: 7.26 ppm; $^{13}$C: 77.16 ppm). Coupling constants are reported in Hertz. Multiplicity is reported with the usual abbreviations (s: singlet, bs: broad singlet, d: doublet, dd: doublet of doublets, ddd: doublet of doublet of doublets, t: triplet, td: triplet of doublets, q: quartet, dq: doublet of quartet, p: pentet, sex: sextet, hept: heptet, m: multiplet).

Exact mass spectra were recorded on a LTQ Orbitrap XL apparatus with ESI ionization. Enantiomeric excesses (ee’s) were determined by Chiral HPLC analysis using a Shimadzu LC-10AD VP HPLC equipped with a Shimadzu SPD-M10A VP diode array detector and by Waters Acquity UPC2 system with PDA detector and QDA mass detector. E-Z photoisomerization experiments were performed using Spectroline model ENC-280C/FE lamp ($\lambda_{max} = 365$ nm, $\pm 30$nm). Unless otherwise indicated, reagents and substrates were purchased from commercial sources and used as received. Solvents not required to be dry were purchased as technical grade and used as received. Dry solvents were freshly collected from a dry solvent purification system prior to use. Inert atmosphere experiments were performed with standard Schlenk techniques with dried (P$_2$O$_5$) nitrogen gas. Grignard reagents were purchased from Sigma-Aldrich and used as received [EtMgBr (3M in Et$_2$O), MeMgBr (3M in Et$_2$O)]. Unless otherwise noted substrates were prepared by literature reported methods (vide infra). Chiral ligand L1 was 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.

5.4.2 Synthesis and Characterizations of Substrates 17 and 18

(E)-4-styrylpyridine (17)

Compound 17 was synthesized according to the literature procedure.$^{17}$ The product was obtained as a white solid after flash-column chromatography (SiO$_2$, pentane:EtOAc, 80:20, v/v). Yield = 63%. The NMR data are in agreement with the one present in literature.$^{18}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.58 (d, $J = 5.1$ Hz, 2H), 7.55 (d, $J = 7.0$ Hz, 2H), 7.44 - 7.34 (m, 5H), 7.31 (d, $J = 16.0$ Hz, 1H), 7.02 (d, $J = 16.3$ Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 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.
(E)-2-styryl-5-(trifluoromethyl)pyridine (18)

Compound 18 was synthesized according to the literature procedure. The product was isolated as a white solid after flash-column chromatography (SiO₂, pentane:EtOAc, 95:5, v/v), Yield = 84%

^1H NMR (400 MHz, CDCl₃) δ 8.85 (s, 1H), 7.90 (d, J = 7.1 Hz, 1H), 7.77 (d, J = 16.0 Hz, 1H), 7.61 (d, J = 7.5 Hz, 2H), 7.49 (d, J = 8.2 Hz, 1H), 7.40 (t, J = 7.4 Hz, 2H), 7.37 – 7.30 (m, 1H), 7.21 (d, J = 16.1 Hz, 1H).

^13C NMR (101 MHz, CDCl₃) δ 158.9, 146.5 (q, J = 4.0 Hz), 136.0, 135.6, 133.7 (q, J = 3.6 Hz), 129.0, 128.8, 127.4, 126.5, 124.3 (q, J = 32.9 Hz), 123.7 (q, J = 271.8 Hz), 121.4.

^19F NMR (376 MHz, CDCl₃) δ -62.2.

HRMS (ESI⁺): m/z calcd. for C₁₄H₁₁F₃N ([M+H⁺]) 250.08381, measured mass: 250.08355

5.4.3 Synthesis and Characterizations of Products 19

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

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr·SMe₂ (0.01 mmol, 10 mol%), and ligand (R,S₉)·L1 (0.012 mmol, 12 mol%) were dissolved in CH₂Cl₂ (1mL/0.1mmol of substrate) and stirred under nitrogen atmosphere for 15 min. Substrate 17 (0.1 mmol, 1 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C and TMSOTf (0.3 mmol, 3 equiv) was added followed by EtMgBr (3M in Et₂O, 0.3 mmol, 3 equiv). After stirring at -78 °C for 16h, the reaction was quenched with MeOH (1 mL) followed by saturated aqueous solution of NH₄Cl and warmed to RT. Reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated on rotary evaporator. Product 19 was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc 80:20, v/v), [94% yield, 93% ee].

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

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

HRMS (ESI⁺): m/z calcd. for C₁₅H₁₈N ([M+H⁺]) 212.14338, found 212.14315

CSP-HPLC: (254 nm, Chiralcel OZ-H, n-heptane:iPrOH = 95:5, 40 °C, 1.0 ml/min.), tᵣ = 9.61 min (major), tₐᵣ = 10.27 min (minor).
5.4.4 Synthesis and Characterizations of Product 20

(S)-2-(2-phenylbutyl)-5-(trifluoromethyl)pyridine

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr-SMe₂ (0.01 mmol, 5 mol%), and ligand (R,S₂)-L1 (0.012 mmol, 6 mol%) were dissolved in Et₂O (1mL/0.1mmol of substrate) and stirred under nitrogen atmosphere for 15 min. Substrate 18 (0.1 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 (0.15 mmol, 1.5 equiv) was added followed by EtMgBr (3M in Et₂O, 0.3 mmol, 1.5 equiv). After stirring at -78 °C for 16h, the reaction was quenched with MeOH (1 mL) followed by saturated aqueous solution of NH₄Cl and warmed to RT. Reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated on rotary evaporator. Product 20 was obtained as pale-yellow oil after flash-column chromatography (SiO₂, pentane:EtOAc 99:1, v/v), [52% yield, 86% ee]

1H NMR (400 MHz, CDCl₃) δ 8.78 (d, J = 2.3 Hz, 1H), 7.79 (dd, J = 8.2, 2.3 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 2.77 (d, J = 7.2 Hz, 2H), 1.84 (hept, J = 6.5 Hz, 1H), 1.40–1.10 (m, 12H), 0.86 (q, J = 7.3 Hz, 6H).

13C NMR (101 MHz, CDCl₃) δ 164.8, 146.0 (q, J = 4.0 Hz), 143.91, 132.9 (q, J = 3.4 Hz), 128.31, 127.68, 126.26, 124.00 (q, J = 3.4 Hz), 123.25,122.3 (q, J = 371.8 Hz) 48.04, 45.57, 28.95, 12.02.

19F NMR (376 MHz, CDCl₃) δ -62.3.

HRMS (ESI⁺): m/z calcd. for C₁₆H₁₇F₃N ([M+H⁺]) 280.13076, found 280.13144

CSP-HPLC: (254 nm, Chiralcel OJ-H, n-heptane:iPrOH = 99.5:0.5, 40 °C, 0.5 ml/min.), tᵣ = 8.18 min (major), tᵣ = 8.64 (minor).

5.4.5 (E)/(Z) Isomerization Studies

Preparation of (Z)-17 by photoisomerization

A solution (E)-17 in 5 screw cap glass vials (each vial contain 25mg in 2.5 mL CH₂Cl₂) was irradiated with 365-nm light [Spectroline model ENC-280C/FE lamp] for 5h (NMR monitoring). The solvent was evaporated in vacuo to provide a mixture of (Z)-17 and (E)-17 in 76:14 ratio. After flash column chromatography (Z)-17 was isolated with 99.6% purity remaining 0.4% was (E)-17 (SiO₂, pentane:EtOAc 80:20 v/v).

1H NMR (CDCl₃, 400 MHz): δ 8.45 (d, J = 5.0 Hz, 2H), 7.27–7.23 (m, 3H), 7.23–7.18 (m, 2H), 7.11 (d, J = 6.1 Hz, 2H), 6.80 (d, J = 12.2 Hz, 1H), 6.50 (d, J = 12.2 Hz, 1H).

13C NMR (CDCl₃, 100.58 MHz): δ 149.9, 145.2, 136.3, 134.2, 128.9, 128.6, 128.0, 127.7, 123.7.
Preparation of \((Z)-18\) by photoisomerization

A solution \((E)-18\) in 5 screw cap glass vials (each vial contain 25mg in 2.5 mL \(\text{CH}_2\text{Cl}_2\)) was irradiated with 365-nm light [Spectroline model ENC-280C/FE lamp] for 24h (NMR monitoring). The solvent was evaporated in vacuo to provide a mixture of \((Z)-18\) and \((E)-18\) in 64:36 ratio. After flash column chromatography \((Z)-18\) was isolated was isolated with 99.0% purity remaining 1.0% was \((E)-18\) (SiO\(_2\), pentane:EtOAc 98:2 v/v).

\(^1\text{H}\) NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.84 (s, 1H), 7.65 (dd, \(J = 8.4, 2.4\) Hz, 1H), 7.35–7.16 (m, 6H), 6.97 (d, \(J = 12.4\) Hz, 1H), 6.71 (d, \(J = 12.5\) Hz, 1H).

\(^{13}\text{C}\) NMR (CDCl\(_3\), 100.58 MHz): \(\delta\) 159.97, 159.96, 146.6 (q, \(J = 4.2\) Hz), 136.2, 135.7, 132.8 (q, \(J = 3.5\) Hz), 129.4, 128.9, 128.9, 128.6, 128.2, 124.5 (q, \(J = 33.0\) Hz), 124.3 (q, \(J = 271.5\) Hz), 123.6.

\(^{19}\text{F}\) NMR (376 MHz, CDCl\(_3\)) \(\delta\) -62.6

Catalytic asymmetric addition of EtMgBr to \((Z)-17\)

The reaction was performed using general procedure A, with 0.1 mmol \((Z)-17\), TMSOTf (0.3 mmol, 3.0 equiv), EtMgBr (3M in Et\(_2\)O, 0.3 mmol, 3.0 equiv), CuBr·SMe\(_2\) (0.01 mmol, 10 mol%), ligand (R,S\(_p\))-L1 (0.012 mmol, 12 mol%) in 1mL CH\(_2\)Cl\(_2\). Product \((R)-22\) was obtained as pale-yellow oil after flash-column chromatography (SiO\(_2\), pentane:EtOAc 90:10 v/v), [72% yield, 42% ee].

\((E)/(Z)\) isomerization experiments of \((Z)-17\) with TMSOTf

\((Z)-17\) (9.06mg, 0.05 mmol) was placed in a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar. After addition of CH\(_2\)Cl\(_2\) (0.5mL) the mixture was cooled to -78 °C and TMSOTf (33.35 mg/ 27.15 μL, 0.15 mmol, 3 equiv) was added. After stirring for 15h at -78 °C the reaction mixture was quenched by adding MeOH (1 mL) followed by addition of saturated aqueous NH\(_4\)Cl solution and warmed to RT. The resulting mixture was extracted with CH\(_2\)Cl\(_2\) (2 x 10mL). Combined organic phases were dried over MgSO\(_4\), filtered and solvents were evaporated. The \((E)/(Z)\) ratio of 17 in the resulting crude mixture was determined by \(^1\text{H}-\text{NMR}\) and was found to be 24:76.

\((E)/(Z)\) isomerization experiments of \((Z)-17\) with EtMgBr

\((Z)-17\) (9.06 mg, 0.05 mmol) was placed in a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar. After addition of CH\(_2\)Cl\(_2\) (0.5mL) the mixture was cooled to -78 °C and EtMgBr (3M in Et\(_2\)O, 50 μL, 0.15 mmol, 3 equiv) was added. After stirring for 15h at -78 °C the reaction mixture was quenched by adding MeOH (1 mL) followed by addition of saturated aqueous NH\(_4\)Cl solution and warmed to RT. The resulting mixture was extracted with CH\(_2\)Cl\(_2\) (2 x 10mL). Combined organic phases were dried over MgSO\(_4\), filtered and solvents were evaporated. The \((E)/(Z)\) ratio of 17 in the resulting crude mixture was determined by \(^1\text{H}-\text{NMR}\) and was found to be 02:98.

\((E)/(Z)\) isomerization experiments of \((Z)-17\) with EtMgBr and TMSOTf

\((Z)-17\) (9.06 mg, 0.05 mmol) was placed in a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar. After addition of CH\(_2\)Cl\(_2\) (0.5mL) the mixture was cooled to -78 °C and TMSOTf (33.35 mg/ 27.15 μL, 0.15 mmol, 3 equiv) and EtMgBr (3M in Et\(_2\)O, 50 μL, 0.15 mmol, 3 equiv) were added. After stirring for 15h at -78 °C the reaction mixture was
quenched by adding MeOH (1 mL) followed by addition of saturated aqueous NH₄Cl solution and warmed to RT. The resulting mixture was extracted with CH₂Cl₂ (2 × 10mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated. The (E)/(Z) ratio of 17 in the resulting crude mixture was determined by ¹H-NMR and was found to be 18:82.

**(E)/(Z) isomerization experiments of (Z)-17 with Cu-SMe₂ and (R, Sₚ)-L1**

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, Cu-SMe₂ (1.025 mg, 0.005 mmol, 0.1 equiv) and (R, Sₚ)-L1 (3.57 mg, 0.006 mmol, 0.12 equiv) were dissolved in CH₂Cl₂ (0.5mL) and stirred under nitrogen atmosphere for 15 min. Substrate (1.0 equiv) (Z)-17 (9.06 mg, 0.05 mmol) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C. After stirring at -78 °C for 16h, the reaction was quenched with MeOH (1 mL) followed by saturated aqueous solution of NH₄Cl and warmed to RT. The resulting mixture was extracted with CH₂Cl₂ (2 × 10mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated. The (E)/(Z) ratio of 17 in the resulting crude mixture was determined by ¹H-NMR and was found to be 02:98.

**(E)/(Z) isomerization experiments of (Z)-17 with CuBr-SMe₂, (R, Sₚ)-L1, TMSOTf, and MeMgBr**

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, Cu-SMe₂ (2.05 mg, 0.01 mmol, 0.1 equiv) and (R, Sₚ)-L1 (7.14 mg, 0.012 mmol, 0.12 equiv) were dissolved in CH₂Cl₂ (1 mL) and stirred under nitrogen atmosphere for 15 min. Substrate (1.0 equiv) (Z)-17 (18 mg, 0.1 mmol, 1 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C. and TMSOTf (66.7 mg/ 54 µL, 0.3 mmol, 3 equiv) was added followed by MeMgBr (2M in Et₂O, 100 µL, 0.3 mmol, 3 equiv). After stirring at -78 °C for 16h, the reaction was quenched with MeOH (1 mL) followed by saturated aqueous solution of NH₄Cl and warmed to RT. The resulting mixture was extracted with CH₂Cl₂ (2 × 10mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated. The (E)/(Z) ratio of 17 in the resulting crude mixture was determined by ¹H-NMR and was found to be 14:86.

**Catalytic asymmetric addition of EtMgBr to (Z)-18**

The reaction was performed using general procedure B, with 0.05 mmol (Z)-18, BF₃OEt₂ (0.075 mmol, 1.5 equiv), EtMgBr (3M in Et₂O, 0.1 mmol, 2.0 equiv), CuBr-SMe₂ (0.005 mmol, 10 mol%), ligand (R, Sₚ)-L1 (0.006 mmol, 12 mol%) in 0.5 mL Et₂O. After 15h at -78 °C reaction reached 34% conversion and product (R)-20 was not isolated and directly injected in HPLC to determine the ee of the reaction that was found to be 76%.

**(E)/(Z) isomerization experiments of (Z)-18 with BF₃OEt₂**

(Z)-18 (12.45mg, 0.05 mmol) was placed in a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar. After addition of Et₂O (0.5mL) the mixture was cooled to -78 °C and BF₃OEt₂ (10.6 mg/ 10 µL, 0.075 mmol, 1.5 equiv) was added. After stirring for 15h at -78 °C the reaction mixture was quenched by adding MeOH (1 mL) followed by addition of saturated aqueous NH₄Cl solution and warmed to RT. The resulting mixture was extracted with CH₂Cl₂ (2 × 10mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated. The (E)/(Z) ratio of 18 in the resulting crude mixture was determined by ¹H-NMR and was found to be 01:99.
(E)/(Z) isomerization experiments of (Z)-18 with EtMgBr

(Z)-18 (12.45 mg, 0.05 mmol) was placed in a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar. After addition of Et₂O (0.5 mL) the mixture was cooled to -78 °C and EtMgBr (3 M in Et₂O, 30 μL, 0.1 mmol, 2.0 equiv) was added. After stirring for 15 h at -78 °C the reaction mixture was quenched by adding MeOH (1 mL) followed by addition of saturated aqueous NH₄Cl solution and warming to RT. The resulting mixture was extracted with CH₂Cl₂ (2 × 10 mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated. The (E)/(Z) ratio of 18 in the resulting crude mixture was determined by ¹H-NMR and was found to be 01:99.

(E)/(Z) isomerization experiments of (Z)-18 with EtMgBr and BF₃·OEt₂

(Z)-18 (12.45 mg, 0.05 mmol) was placed in a heat dried Schlenk tube equipped with rubber septum and magnetic stirring bar. After addition of Et₂O (0.5 mL) the mixture was cooled to -78 °C and BF₃·OEt₂ (10.6 mg/10 μL, 0.075 mmol, 1.5 equiv) and EtMgBr (3 M in Et₂O, 30 μL, 0.1 mmol, 2.0 equiv) were added. After stirring for 15 h at -78 °C the reaction mixture was quenched by adding MeOH (1 mL) followed by addition of saturated aqueous NH₄Cl solution and warming to RT. The resulting mixture was extracted with CH₂Cl₂ (2 × 10 mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated. The (E)/(Z) ratio of 18 in the resulting crude mixture was determined by ¹H-NMR and was found to be 04:96.

(E)/(Z) isomerization experiments of (Z)-3b with Cu·SMe₂ and (R, Sₚ)-L1

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, Cu·SMe₂ (1.025 mg, 0.005 mmol, 0.1 equiv) and (R, Sₚ)-L1 (3.57 mg, 0.006 mmol, 0.12 equiv) were dissolved in Et₂O (0.5 mL) and stirred under nitrogen atmosphere for 15 min. Substrate (1.0 equiv) (Z)-18 (12.45 mg, 0.05 mmol) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C. After stirring at -78 °C for 16 h, the reaction was quenched with MeOH (1 mL) followed by saturated aqueous solution of NH₄Cl and warmed to RT. The resulting mixture was extracted with CH₂Cl₂ (2 × 10 mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated. The (E)/(Z) ratio of 18 in the resulting crude mixture was determined by ¹H-NMR and was found to be 05:95.

(E)/(Z) isomerization experiments of (Z)-18 with Cu·SMe₂, (R, Sₚ)-L1, MeMgBr and BF₃·OEt₂

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, Cu·SMe₂ (1.025 mg, 0.005 mmol, 0.1 equiv) and (R, Sₚ)-L1 (3.57 mg, 0.006 mmol, 0.12 equiv) were dissolved in Et₂O (0.5 mL) and stirred under nitrogen atmosphere for 15 min. Substrate (1.0 equiv) (Z)-18 (12.45 mg, 0.05 mmol) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C. After stirring for 15 min. at RT the reaction mixture was cooled to -78 °C. After stirring for 16 h the reaction mixture was quenched with MeOH (1 mL) followed by saturated aqueous solution of NH₄Cl and warmed to RT. The resulting mixture was extracted with CH₂Cl₂ (2 × 10 mL). Combined organic phases were dried over MgSO₄, filtered and solvents were evaporated. The (E)/(Z) ratio of 18 in the resulting crude mixture was determined by ¹H-NMR and was found to be 05:95.
5.4.6 NMR Studies

In order to determine the activation mode of pyridines (17 and 18) in the presence of different Lewis acids, a set of experiments was carried out. Complexes of 17 with TMSOTf, TMSCl, BF₃·Et₂O, and EtMgBr, and 18 with BF₃·Et₂O and EtMgBr were prepared separately by following the general procedure below and analyzed by ¹H NMR spectroscopy.

5.4.7 General Procedure for Preparation of Pyridine-LA and Pyridine-EtMgBr Complexes

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, pyridine substrate 17 or 18 (0.1 mmol, 1 equiv) was dissolved in CD₂Cl₂ (1 mL) under N₂ atmosphere at room temperature, the reaction mixture was then cooled to -78 °C and Lewis acid or EtMgBr (0.15-0.2 mmol, 1.5-2.0 equiv) was added to this solution. After stirring for 10 minutes, the resulting reaction mixture was rapidly transferred by syringe into a dry NMR tube under N₂ atmosphere at -78 °C. A new species formed was immediately checked by ¹H NMR spectroscopy at -60 °C.

17-TMSOTf complex was prepared by following the general procedure above, with 17 (18.1 mg, 0.1 mmol) in CD₂Cl₂ (1 mL) and TMSOTf (36 µL, 0.2 mmol). After stirring for 10 minutes the resulting turbid reaction mixture was immediately measured by ¹H NMR spectroscopy at -60 °C.

17-TMSCl complex was prepared by following the general procedure above, with 17 (18.1 mg, 0.1 mmol) in CD₂Cl₂ (1 mL) and TMSCl (26 µL, 0.2 mmol). After stirring for 10 minutes the resulting reaction mixture was immediately measured by ¹H NMR spectroscopy at -60 °C.

17-BF₃·Et₂ complex was prepared by following the general procedure above, with 17 (18.1 mg, 0.1 mmol) in CD₂Cl₂ (1 mL) and BF₃·Et₂ (25 µL, 0.2 mmol). After stirring for 10 minutes the resulting reaction mixture was immediately measured by ¹H NMR spectroscopy at -60 °C.

17-EtMgBr complex was prepared by following the general procedure above, with 17 (18.1 mg, 0.1 mmol) in CD₂Cl₂ (1 mL) and EtMgBr (60 µL, 0.2 mmol). After stirring for 10 minutes the resulting reaction mixture was immediately measured by ¹H NMR spectroscopy at -60 °C.

18-BF₃·Et₂ complex was prepared by following the general procedure above, with 18 (24.9 mg, 0.1 mmol) in CD₂Cl₂ (1 mL) and BF₃·Et₂ (19 µL, 0.15 mmol). After stirring for 10 minutes the resulting reaction mixture was immediately measured by ¹H NMR spectroscopy at -60 °C.

18-EtMgBr complex was prepared by following the general procedure above, with 18 (24.9 mg, 0.1 mmol) in CD₂Cl₂ (1 mL) and EtMgBr (60 µL, 0.2 mmol). After stirring for 10 minutes the resulting reaction mixture was immediately measured by ¹H NMR spectroscopy at -60 °C.
5.5 Bibliography


