Highly enantioselective catalytic synthesis of chiral pyridines

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General methods to prepare chiral pyridine derivatives are greatly sought after due to their significance in medicinal chemistry. Here, we report highly enantioselective catalytic transformations of poorly reactive β-substituted alkenyl pyridines to access a wide range of alkylated chiral pyridines. The simple methodology involves reactivity enhancement via Lewis acid (LA) activation, the use of readily available and highly reactive Grignard reagents, and a copper-chiral diphosphine ligand catalyst. Apart from allowing the introduction of different linear, branched, cyclic, and functionalised alkyl chains at the β-position of alkenyl pyridines, the catalytic system also shows high functional group tolerance.
Pyridines are among the most important classes of heterocyclic moieties, and occur in many bioactive molecules, such as natural products, pharmaceuticals, and agrochemicals. Furthermore, pyridines are also useful structural motifs in various chemical transformations and they are widely employed as ligands. Pyridine is the single most commonly found nitrogen-containing aromatic heterocycle among all U.S. FDA approved pharmaceuticals and is present in more than 60 currently marketed drugs. As a result of their immense importance, methods to access different pyridine derivatives have been pursued for decades. Although elaboration of the pyridine ring remains one of the most common and straightforward approaches, exploitation of the pyridine moiety to activate adjacent olefins towards enantioselective conjugate addition (CA) of nucleophiles has recently gained prominence.

Highly enantioselective copper catalysed CA of hydride nucleophiles to β,β-disubstituted alkenyl pyridines was reported by Lam and co-workers. However, when carbon nucleophiles are considered, non-enantioselective CAs of carbon nucleophiles to unsubstituted vinylpyridines are well known, whereas examples of general methodologies for enantioselective additions to β-substituted alkenyl pyridines are rare. The diminished reactivity of these β-substituted alkenyl pyridines that lies at the heart of this deficiency is a persistent issue, because of the low activation of the conjugated alkene by the pyridine ring. Consequently, only a few examples of enantioselective functionalisation of an alkenyl pyridine have been reported, and these all require the use of activated pyridines, higher temperatures, and a Rh-catalyst. Moreover, these methodologies focus on arylation and do not allow alkylation. As the poor electrophilicity of alkenyl pyridines is one of the major problems for nucleophilic additions, we anticipated that the use of highly reactive Grignard reagents might be helpful to overcome the low reactivity of these substrates. This idea was further supported by the nickel-catalysed CA of aryl Grignard reagents to alkenyl pyridine.

| Entry | Solvent | L, mol% | Lewis acid, equiv. | Conv. (%) | ee (%) |
|-------|---------|---------|-------------------|-----------|--------|
| 1     | DCM     | L1, 6   | BF₃OEt₂, 1.1      | 0         | —      |
| 2     | DCM     | L1, 6   | BF₂Ph₂, 1.1       | 0         | —      |
| 3     | DCM     | L1, 6   | TMSOTf, 1.5       | 89        | 89     |
| 4     | DCM     | L1, 6   | TMSOTf, 2.0       | 85        | 85     |
| 5     | DCM     | L1, 6   | TMSOTf, 3.0       | 91        | 89     |
| 6     | DCM     | L1, 12  | TMSOTf, 1.5       | 91        | 92     |
| 7     | DCM     | L1, 12  | TMSOTf, 2.0       | 95        | 93     |
| 8     | DCM     | L1, 12  | TMSOTf, 3.0       | 100       | 93     |
| 9     | Et₂O    | L1, 12  | TMSOTf, 3.0       | 62        | 95     |
| 10    | MTBE    | L1, 12  | TMSOTf, 3.0       | 67        | 96     |
| 11    | Toluene | L1, 12  | TMSOTf, 3.0       | 79        | 87     |
| 12    | DCM     | L2, 12  | TMSOTf, 3.0       | 76        | 45     |
| 13    | DCM     | L3, 12  | TMSOTf, 3.0       | 93        | 81     |
| 14    | DCM     | L4, 12  | TMSOTf, 3.0       | 95        | 90     |

*a; or 12 mol% of L was used in combination with 5 or 10 mol% of CuBr·SMe₂ respectively.
bEquivalents of EtMgBr used correspond to that of the Lewis acid.
cDetermined by ¹H NMR spectroscopy.
dDetermined by chiral HPLC.
reported in 1998, providing good yields although nearly racemic products20.

Here we present a Cu-catalysed, highly enantio- and chemoselective alkylation protocol of poorly reactive alkenyl pyridines using Lewis acid (LA) activation and Grignard reagents as nucleophiles. Various pyridine derivatives can undergo CA of a wide range of Grignard reagents, both linear and branched. The catalytic system shows a remarkable functional group tolerance, providing a handle

![Diagram](image_url)

**Table 2 Substrate scope**

| Entry | Substrate | Conditions | Yield (%) | ee (%) |
|-------|-----------|------------|-----------|--------|
| 1     | 1a        | A          | 2a        | 94     |
|       |           |            | 2a        | 93     |
| 2     | 1b        | A          | 2b        | 87     |
|       |           |            | 2b        | 89     |
| 3     | 1c        | B          | 2c        | 82     |
|       |           |            | 2c        | 97†    |
| 4     | 1d        | A          | 2d        | 86     |
|       |           |            | 2d        | 93     |
| 5     | 1e        | A          | 4a        | 74     |
|       |           |            | 4a        | 89     |
| 6     | 1f        | B          | 4b        | 52     |
|       |           |            | 4b        | 86     |
| 7     | 1g        | B          | 4c        | 60     |
|       |           |            | 4c        | 99†    |
| 8     | 3a        | B          | 4d        | 93     |
|       |           |            | 4d        | 89     |
| 9     | 3b        | B          | 4e        | 64     |
|       |           |            | 4e        | 87     |
| 10    | 3c        | B          | 4f        | 59†    |
|       |           |            | 4f        | 95     |
| 11    | 3d        | B          | 4g        | 75†    |
|       |           |            | 4g        | 99     |

*Conditions A: TMSOTf (3 equiv.) and EtMgBr (3 equiv.); conditions B: B3F5Et2O (1.5 equiv) and EtMgBr (1.5 equiv.)

†Reported yields are for isolated products

‡Determined by chiral HPLC

The absolute configurations of products were determined on the basis of single-crystal X-ray diffraction analysis of compound 2a† (see Supplementary Information)

††EtMgBr diluted in toluene and added dropwise over 2 h

‡‡of corresponding alcohol 2ε after deprotection

§§5 mol% of catalyst used

|| of the corresponding ether 10

‖Small amount of unreacted substrate (≤9%) is not separable from product by chromatography, yields are calculated by purity of product in the mixed fraction by 1H NMR
for further product transformations. Finally, mechanistic studies that allow to disclose the reaction pathway are presented as well.

Results

Optimisation of reaction conditions. We started out our investigations by evaluating copper catalysed conjugate alkylation of alkenyl pyridines with Grignard reagents. 4-Styryl pyridine 1a and EtMgBr served as model reaction for the initial screening of suitable conditions (Table 1). Substrate 1a was tested in the presence of a catalytic system derived from CuBr·SMe$_2$ salt and diphosphine ferrocenyl ligand L1 within the temperature range of −78 °C to ambient temperature. Analysis of the crude reaction mixture by $^1$H NMR revealed no conversion of the starting material, confirming the markedly lower reactivity of β-substituted alkenyl pyridines towards nucleophilic addition compared to vinylpyridines. Recently, our group developed a protocol that employs BF$_3$·Et$_2$O as LA to activate poorly reactive heteroaromatic compounds towards nucleophilic addition of Grignard reagents. We applied a similar protocol to 4-styryl pyridine 1a, but, once again, no product was detected (Table 1, entry 1). We envisioned that stronger activation of pyridine substrates could be achieved by using TMSOTf as LA to tackle the reactivity issue.

Indeed, screening of various LAs revealed that stronger activation of alkenyl pyridine does allow Grignard addition (Table 1, entries 1–5), with TMSOTf the optimal choice, providing alkyalted pyridine product 2a with 89% conversion and 89% ee (Table 1, entry 3). Importantly, TMSOTf can promote the addition reaction in the absence of the copper catalyst as well. To reach full conversion in the catalytic reaction and to minimise the effect of the non-catalytic TMSOTf-promoted pathway on the final enantioselectivity of the reaction, we studied the effect of the stoichiometry of the copper catalyst, TMSOTf and Grignard reagents (Table 1, entries 4–8). Although the enantioselectivity remained largely unchanged, full conversion was reached only when 3 equiv. of EtMgBr and TMSOTf was used (Table 1, entry 5). On the other hand, carrying out the reaction with a two-fold increase in the Cu-catalyst loading, resulted in an increase of the enantioselectivity to 93% (Table 1, entries 6–8).

Having established the optimal LA and catalyst loading for the reaction, we investigated the effect of different solvents next. All solvents tested (DCM, Et$_2$O, MTBE, and toluene) were well tolerated by the alkylation protocol, providing product 2a with excellent ee’s (Table 1, entry 8 vs entries 9–11). On the other hand, full conversion towards the addition product was reached only in DCM, which prompted us to carry out chiral ligand optimisation in this solvent.

Among the different chiral ligands studied (for detailed ligand screening, see Supplementary Table 1) all the diphosphine ferroenyl ligands (L1–L4) were able to promote the reaction to a different extent. Ligands L1, L3 and L4 showed superior reactivity, delivering the desired product in excellent conversion and ee (Table 1, entries 8, 13–14). As ligand L1 performed slightly better than L3 and L4, we adopted the following optimised conditions for further substrate scope study: CuBr·SMe$_2$ (10 mol %), (R,S$_p$)-L1 (12 mol%), Grignard reagent (3 equiv.), TMSOTf (3 equiv.), in DCM solvent for 16 h at −78 °C.

Pyridine substrate scope. For studying the substrate scope we chose the reaction between 4-alkenyl pyridines (1a–1d) and 2-alkenyl pyridines (3a–3g) with EtMgBr (Table 2). 4-Alkenyl pyridines 1a–1d readily underwent the nucleophilic addition reaction, irrespective of the β-substituent on the double bond (Table 2, entries 1–4). Alkyl and aryl substituents, both electron rich and electron poor, at the β-position were well tolerated, affording the alkyalted products 2a–2d in excellent isolated yields and enantiopurities (Table 2, entries 1–4). When 3-octenyl pyridine, 2- styryl pyridine or 2-octenyl pyridine were subjected to our optimised reaction conditions, no conversion towards the
addition product was noted (Table 2 scheme). Although the poor reactivity of 3-octenyl pyridine can be attributed to the lack of resonance activation of the adjacent olefin moiety upon coordination of the substrate to the LA, the lack of reactivity of the latter two is more surprising. Interestingly, introducing a tert-butylidimethylsilyl ether (OTBDS) group at the 8-position enhanced the reactivity sufficiently, thus providing corresponding product 4a with high yield and enantioselectivity (Table 2, entry 5).

As expected, alkenyl pyridines with an electron-withdrawing group in the aromatic ring (Tables 2, 3c) required milder activation. In this case, the use of 1.5 equiv. of BF₃·OEt₂ instead of 3.0 equiv. of TMSOTf provided the corresponding products 4b and 4c with good yields and excellent enantioselectivities (Table 2, entries 6, 7).

We were particularly interested in performing these reactions with functionalised pyridines, which can provide a handle for further modification after Grignard addition. For this purpose, several alkenyl pyridine substrates with various functional groups were prepared (Tables 2, 3d–3g) and subjected to the reaction protocol using BF₃·OEt₂.

Grignard reagents are often considered incompatible with reactive functional groups. Nevertheless, the excellent chemoselectivity of our protocol allowed us to perform addition reactions not only to alkylidene pyridines that contain halogens (Tables 2, 3f, 3g), but also to those containing highly reactive ester and cyano groups (Tables 2, 3d, 3e) in the aromatic ring. The corresponding alkylated products 4d–4g were obtained with good to excellent yields and ee’s (Table 2, entries 8–11).

**Grignard reagent scope.** To assess the nucleophile scope, substrates 1a and 1d were chosen as model compounds (Table 3). Addition of all tested linear Grignard reagents afforded the products 2a, 5a and 5b with good to excellent yields (75–94%) and ee’s (93–95%), independent of the chain length (Table 3, entries 1–3). The sterically demanding α-, β-, and γ-branched Grignard reagents were also tolerated, providing products 5c–5e with moderate to good yields (54–65%) (Table 3, entries 4–6).

Particularly the γ- and α-branched Grignard reagents delivered products 5c and 5e with high ee’s of 97 and 89%, respectively (Table 3, entries 4 and 6), whereas the β-branched Grignard provided product 5d with moderate ee (64%; Table 3, entry 5). Grignard reagents bearing olefinic or aromatic substituents were also well tolerated, affording the corresponding products 5f, 5g and 5h with good yields and excellent ee’s (Table 3, entries 7–9).

Next, we investigated the reaction between 4-alkenyl pyridine and MeMgBr, the least reactive Grignard reagent, but the most interesting for pharmaceutical applications.

We were pleased to find that, thanks to the substantial activation provided by TMSOTf, the reaction proceeded with 87% conversion within 5 h at 0 °C. The product was isolated with excellent ee (93%) and a moderate yield of 50% (Table 3, entry 10).

On the other hand, addition of PhMgBr resulted in a complex reaction mixture. Changing from ligand L1 to L10 allowed to obtain the addition product 5j with good yield, but unfortunately as a racemate (Table 3, entry 11). This result is in striking contrast with the 89% enantioselectivity obtained in our previous work for the addition of PhMgBr to alkylidene benzoxazole 21 and could be attributed to an inability of the Cu-catalysed addition of PhMgBr to outcompete the LA promoted non-catalysed addition.

**Practical aspects and products functionalisation.** To evaluate the robustness of our methodology, a series of experiments was carried out for the addition of EthMgBr to 1a (Fig. 2a). Performing the reaction on a 30-fold larger scale (3 mmol vs. 0.1 mmol) did not affect the outcome of the reaction and product 2a was isolated with the same excellent yield (94%) and ee (94%) as for the 0.1 mmol reaction. Remarkably, the catalyst recovered (as a copper complex) from this reaction could be recycled with only minor deviations from the original results. Moreover, to assess the effect of temperature on the reaction and on the compatibility of the LA and the Grignard, the reaction was carried out at room temperature. To our surprise, the reaction proceeded to completion in 35 min and the product 2a was isolated with 91% yield,
although a significant drop in ee from 94 to 79% was noted. Assuming that the drop in enantioselectivity is due to the competing non-catalysed blank reaction, we performed the reaction at 0 °C, which improved the ee to 83%. Finally, we found that TMSBr is also an effective LA for this transformation, allowing the reaction to be carried out at room temperature and affording the final product with 73% yield and 91% ee (Fig. 2a).

Owing to the high functional group tolerance of our catalytic system, we were able to perform further synthetic elaborations of our chiral pyridine products (Fig. 2b). Piperidine derivative 6 was prepared quantitatively by selectively reducing the pyridine ring in 2a in the presence of Pd catalyst and molecular hydrogen. The tetracyclic ring is another heterocycle often encountered in the structures of approved pharmaceuticals. To gain insight into the reaction mechanism, a series of experiments and NMR spectroscopic studies were carried out.

Ung treatment of 4g with ethyl acrylate in the presence of Pd catalyst, the corresponding Heck coupling product 8 was obtained with good yield. Moreover, using 4g it is possible to achieve direct functionalisation of the pyridine ring (product 9) using the protocol developed by Knochel and co-workers. Another direct functionalisation of the pyridine ring of 4c, leading to the formation of pyridyl-ether 10 through pyridyl-phosphonium salt, could be achieved using a very recent methodology developed by McNally and co-workers.

Mechanistic studies. The mechanism of this LA promoted Cu-catalysed addition of Grignard reagents to alkenyl pyridines might follow the same pathway as has been proposed for non-catalytical CA of organocuprates to α,β-unsaturated carbonyl compounds. This implies formation of a reversible copper-alkyl π-complex, followed by oxidative addition to form a Cu (III)-species, and reductive elimination to form the addition product enolate. Our catalytic system employs reagents and reactions conditions similar to those used for CAs to carbonyl compounds, but contrary to these, alkenyl pyridines are unreactive towards organometallics in the absence of LA, even at non-cryogenic conditions. Furthermore, if the addition to alkenyl pyridines follows the same pathway, the aromatics of the pyridines will be altered in several intermediate species. The necessity of LA to accomplish enantioselective CA to alkenyl pyridines adds another level of mechanistic complexity. To gain insight into the reaction mechanism, a series of experiments and NMR spectroscopic studies were carried out.

The experimental data discussed so far demonstrate that TMSOTf is the best LA for 4-substituted alkenyl pyridines, whereas BF₃·Et₂O is the most suitable LA for 2-substituted alkenyl pyridines. In addition, we found that no reaction occurs with non-activated 2-substituted alkenyl pyridines in the presence of either LA. Only after introducing an electron-withdrawing group (EWG) in the pyridine ring, CA occurs in the presence of BF₃·Et₂O (Table 2, entries 6–11). In contrast, using TMSOTf as LA, full conversion to side products (predominantly derived from
the attack to the pyridine ring) occurs. On the other hand, non-activated 4-substituted alkylpyridine can only be converted to the CA product using TMSOTf (Table 2, entries 1, 2 and 4). This trend was further supported by the results obtained upon subjecting substrate 12, which contains both a 4- and a 2-substituted pyridine ring, to the CA reaction (Fig. 3a). In the presence of TMSOTf the major product (13) corresponds to CA with respect to the 4-pyridine site, whereas in the presence of BF3·Et2O the products resulting from CA with respect to both the 4- and 2-pyridine sites (13 and 14, respectively) were observed in a 10:1 ratio. These results clearly indicate that 4-substituted pyridine is intrinsically more reactive towards CA than its 2-substituted analogue.

Further confirmation of the reactivity of pyridine substrates and the effect of LAs was obtained from 1H NMR spectroscopic studies (for details see Supplementary Methods). We investigated the interaction between various reagents (LAs and EtMgBr) and alkylpyridine substrates 1a and 3b at −60 °C (Supplementary Figs. 98 and 99). In all the mixed samples the signals corresponding to the pyridine are shifted with respect to the pure substrate sample. On the basis of the shifts of olefinic protons for substrate 1a upon mixing with either TMSOTf, BF3·Et2O, TMSCl or EtMgBr (1–2 equiv.) we can rank these reagents in terms of their activating Lewis acidic strength as: TMSOTf > BF3·Et2O > TMSCl > EtMgBr. Similar trends were observed for substrate 3b.

To study the effect of the strength and bulkiness of LAs on the CA of EtMgBr to substrate 1a, two sets of experiments were carried out, either in the presence or the absence of the chiral Cu-catalyst (Table 4). As disclosed above, in either case no conversion occurs when using BF3·Et2O as LA, whereas full conversion is observed for TMSOTf (Table 4, compare entries 1–4). The enantioselectivity of 93% obtained with TMSOTf is particularly remarkable, as the LA promoted background reaction in the absence of a copper catalyst is complete at −78 °C in 4 h. Varying the counterion of the silicon based LA allowed a closer look at the LA strength and confirmed that with the very weak TMSCl and somewhat stronger TMSBr no conversion was observed after 15 h without catalyst (Table 4, entries 5 and 6). Remarkably though, in the presence of the Cu-catalyst full conversion to the CA product was observed with TMSBr (Table 4, entry 8) and 60% conversion with TMSCl (Table 4, entry 7) 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 4, entries 9–11). To our surprise, an increase of steric bulk at the silicon atom resulted in decreased enantioselectivity: when moving from TMS- to triethylsilyl (TES-), tert-butyldimethylsilyl (TBS-) and finally to tert-butyldiphenylsilyl (TBDPS) substituted triflates, the ee dropped from 93 to 62% (Table 4, entries 3, 9–11). However, 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 4, entry 12) shows that the 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 reactions using TBS-, TBDMS- and TBDPS-chlorides at both −78 °C and 0 °C did not give any substrate conversion (Table 4, entry 13). However, after screening of various LAs and conditions we found a set of experiments that
settles this matter (Table 4, entries 14–16). At 0 °C the catalysed reaction with TMSCl gives an ee of 91% (Table 4, entry 16), whereas the same reaction with TESCl yields an ee of 82% (Table 4, entry 14). 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. Taken together, these results prove that the bulkiness of the LA affects both the enantioselectivity and the reactivity adversely and thus imply that the LAs are involved in both the stereo- and rate-determining step.

The geometry of alkenes is another important parameter, both for their reactivity and selectivity in addition reactions. Furthermore, when starting from less stable (Z)-alkenes, isomerisation 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 1a and 3b in the presence of TMSOTf and BF3·OEt2, respectively, was studied (Supplementary Table 2). When subjected to (Z)-1a and (Z)-3b to the optimised reaction conditions, the enantioselectivities obtained in both reactions were lower than with (E)-1a and (E)-3b. Although the reduction in ee in the catalytic reaction could be related to the partial isomerisation of the corresponding (Z)-substrates’ double bond during the reaction, subsequent additional control experiments proved that the decreased enantioselectivity is intrinsic to the (Z)-geometry of the substrate and not due to (Z)-(E) isomerisation. This is at odds with our previous findings for Cu-catalysed CA to other N-containing alkylbenzothiazole caused by all reaction components in combination, thus supporting CuI/CuIII redox chemistry with reversible formation of π- to σ-Cu-complexes responsible for substrate isomerisation. The lack of Cu-mediated isomerisation in the present case does not rule out this mechanism, but might be suggestive of other possibilities.

Finally, 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 or boron enolate for BF3·OEt2). In the case of Cu-catalysed CA of EtMgBr to substrate 1a in the presence of TMSOTf, we only observed the formation of silyl-enolate (Supplementary Fig. 104). In the case of CA to 2-alkenyl pyridine substrate 3b using BF3·OEt2, our efforts to characterise the product structure before quenching of the reaction were hampered by severely broad signals observed in 1H NMR.

The information gathered during these investigations allows several inferences to be made regarding the mechanism of our catalytic system as well as a rationalisation of its behaviour.

The presence of LA is a necessary condition to accomplish enantioselective CA to alkynyl pyridines. The fact that LA promotes not only Cu-catalysed, but in several instances also non-catalytic background addition, makes it difficult to elucidate its role precisely. LA additives have been known to accelerate CA of organocopper reagents by (Z)-(E) isomerisations observed in CA of organocopper reagents using (Z)-enones and (Z)-enolates, as well as by kinetic isotope effect studies. With respect to the role of TMSCl several hypotheses were raised, namely silylation of π-complex to form silyl enol ether of σ-complex, by Corey32, 33, LA activation of the enone substrate, by Kuwajima34, and stabilisation of the σ-complex by the chloride of TMSCl, by Snyder and Bertz36. Kinetic isotope experiments by Singleton and co-workers5 resolved this question for the systems studied, with the data consistent with rate-limiting silylation of an intermediate π-complex. This also explains the lack of (Z)-(E)-isomerisations observed in the 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 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.
catalytic cycle from the start of the reaction, through complexation with the pyridine substrate (Supplementary Figs. 98 and 99). In principle steps 1–3 (Fig. 3) 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-determining, and the lack of isomerisation caused by LA/Cu/RMgBr does not distinguish between the steps. On the other hand, if the reductive elimination (Fig. 3, step 3) is the rate-limiting step, acceleration by the LA could prevent accumulation of σ-complex 18, thus quickly converting it to the final azo-enate product 19 and preventing any Cu-mediated isomerisation to occur. Although steps 1 and 2 cannot be excluded, we currently believe that the reductive elimination is the rate- and stereo-determining step, facilitated by the presence of LA in the σ-complex 18 and leading to the formation of a stable azo-enate 19. It is likely that the bulkiness of the LA affects the stability of non-aromatic intermediates 18 and product enolate 19 with the smallest LA being the most stable and in this manner contributes in both the reactivity and enantioselectivity. If the reductive elimination is the rate-limiting step, the rate of the reaction should also be dependent on the rate of re-forming the active catalyst 15. If this process occurs simultaneously with the reductive elimination process it will also be affected by the bulkiness of the LA in the intermediate 18 with the smallest LA allowing the fastest reaction.

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

Using NMR-guided spectroscopic studies, as well as variation of reaction parameters, we were able to identify that Cu-catalysed addition to alkenyl pyridines proceeds through a CA mechanism leading to azo-enate products. We established that LA is involved in the catalytic cycle from the start of the reaction, and that its strength and bulkiness affect both the reactivity and the enantioselectivity of the CA, respectively. Furthermore, studies on the olefin geometry showed that Cu-induced (Z)–(E)-isomerisation does not occur in this catalytic system.

All together, these results prove that the reaction follows the common pathway of Cu-catalysed CA of organometallics and that the bulkiness of LAs affects both the enantioselectivity and the reactivity adversely, thus implying that the LAs are involved in both the stereo- and rate-determining step of the reaction.

Methods
General procedure A Addition to 4-alkenyl pyridines. In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr-SMe2 (0.10 equiv), and ligand (R,S)–L1 (0.12 equiv) were dissolved in CH2Cl2 (1 mL/0.1 mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (1.0 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to −78 °C and BF₃·OEt2 (1.5 equiv) was added followed by RMgX (3.0 equiv.). 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. Reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL). Combined organic phases were dried over MgSO₄ and 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.

General procedure B for the addition to 2-alkenyl pyridines. In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr-SMe2 (0.10 equiv), and ligand (R,S)–L1 (0.12 equiv) were dissolved in Et₂O or CH₂Cl₂ (1 mL/0.1 mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (1.0 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to −78 °C and BF₃·OEt2 (1.5 equiv) was added followed by RMgX (1.5 equiv.). 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. Reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL). Combined organic phases were dried over MgSO₄, 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.

General procedure C for the synthesis of racemic products. In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr-SMe2 (0.10 equiv), and (±)-BINAP (0.12 equiv) were dissolved in CH₂Cl₂ (1 mL/0.1 mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (1.0 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to −78 °C and TMSOTf or BF₃·OEt2 (3.0 equiv) was added followed by RMgX (1.5–3.0 equiv). 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. Reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL). Combined organic phases were dried over MgSO₄, 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. Unless otherwise noted all products were isolated as pale-yellow oil; for liquid/oily substrates, CuBr-SMe2 and ligand (R,S)–L1 were dissolved in 0.7 mL of Et₂O/CH₂Cl₂, whereas the remaining 0.3 mL of Et₂O/CH₂Cl₂ was employed to transfer the substrate in the reaction Schlenk tube.

Data availability
The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information files. For the experimental procedures, additional mechanistic studies, spectroscopic and physical data of compounds, see Supplementary Methods. For NMR and HPLC analysis of the compounds in this article, see Supplementary Figs. 1–156. For ligands screening and isomerisation studies see Supplementary Tables 1 and 2 respectively. The CCDC 1532252 (2a’ prepared from 2a, see Supplementary Note 2) contains the supplementary crystallographic data for this paper (Supplementary file). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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References
1. Wu, Y.-J. Heterocycles and medicine: a survey of the heterocyclic drugs (eds Majumdar, K. C. & Chattopadhyay, S. K.) 63 (Wiley-VCH Verlag, 2012).
2. Akhtar, J., Khan, A. A., Ali, Z., Haider, R. & Shahar Yar, M. Structure-activity relationship (SAR) study and design strategies of nitrogen-containing heterocyclic moieties for their anticancer activities. Eur. J. Med. 125, 143–149.
3. Kiuru, P. & Yli-Kaushalamo, J. P. in Heterocycles in Natural Product Synthesis (eds Majumdar, K. C. & Chattopadhyay, S. K.) 63–95 (Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2011).
4. Guan, A.-Y., Liu, C.-L., Sun, X.-F., Xie, Y. & Wang, M.-A. Discovery of pyridine-based agrochemicals by using intermediate derivatization methods. Bioorg. Med. Chem. 24, 342–353 (2016).
5. Glorius, F., Spielkamp, N., Holle, S., Goddard, R. & Lehmann, C. W. Efficient asymmetric hydrogenation of pyridines. Angew. Chem. Int. Ed. 43, 2850–2852 (2004).
6. Henry, G. D. De novo synthesis of substituted pyridines. Tetrahedron 60, 6083–6086 (2004).
7. Bagley, M. C., Glover, C. & Merritt, E. A. The Bohlmann-Rahtz pyridine synthesis: from discovery to applications. Synlett 16, 2459–2482 (2007).
8. Hill, M. D. Recent strategies for the synthesis of pyridine derivatives. Chem. Eur. J. 16, 12052–12062 (2010).
9. Kålah, N. L. & Beer, P. D. Pyridine and pyridinium-based anion receptors. Top Heterocycl. Chem. 24, 301–340 (2010).
10. Chelucci, G. Metal-complexes of optically active amino- and imino-based pyridine ligands in asymmetric catalysis. Coord. Chem. Rev. 257, 1887–1932 (2013).

11. Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J. Med. Chem. 57, 10257–10274 (2014).

12. Goetz, A. E. & Garg, N. K. Regioselective reactions of 3,4-pyridynes enabled by the arylene distortion model. Nat. Chem. 5, 54–60 (2013).

13. Pozharskii, A. F., Soldatenkov, A. & Katritzky, A. R. (eds) Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications, 2nd edn (Wiley, New York, 2011).

14. Best, D. & Lam, H. W. C jailed aromatic heterocycles as activating groups in enantioselective catalysis. J. Org. Chem. 79, 831–845 (2014).

15. Hepburn, H. B. & Melchiorre, P. Bronsted acid-catalyzed CA of photochemically generated α-amino radicals to alkenylpyridines. Chem. Commun. 52, 3520–3523 (2016).

16. Rupnicki, L., Saxena, A. & Lam, H. W. Aromatic heterocycles as activating groups for asymmetric CA reactions. Enantioselective copper-catalyzed reduction of 2-alkenylheteroarenes. J. Am. Chem. Soc. 131, 10386–10387 (2009).

17. Klump, D. A. CAs to vinyl-substituted aromatic N-heterocycles. Synlett 23, 1590–1604 (2012).

18. Saxena, A. & Lam, H. W. Enantioselective rhodium-catalyzed arylation of electron-deficient alkenylarenes. Chem. Sci. 2, 2326–2331 (2011).

19. Friedman, A. A., Panteleev, J., Tsoung, J., Huynh, V. & Lautens, M. Rh/Pd catalysis with chiral and achiral ligands: domino synthesis of azahydrobenzoxepines. Angew. Chem. Int. Ed. 52, 9755–9758 (2013).

20. Houpis, I. N. et al. Ni-catalyzed nucleophilic CAs of Grignard and organozinc reagents. Entrainment in the σ–π continuum. Tetrahedron Lett. 54, 1185–1195 (1998).

21. Jumde, R. P., Lanza, F., Veenstra, M. J. & Harutyunyan, S. R. Catalytic asymmetric addition of Grignard reagents to alkenyl-substituted aromatic N-heterocycles. Science 352, 433–437 (2016).

22. Chen, Q., Mollat du Jourdin, X. & Knochel, P. Transition-metal-free BF₃-mediated regioselective direct alkylation and arylation of functionalized pyridines using Grignard or organozinc reagents. J. Am. Chem. Soc. 135, 4958–4961 (2013).

23. Hilton, M. C., Dolewski, R. D. & McNally, A. Selective functionalization of pyridines via heterocyclic phosphonitrides. J. Am. Chem. Soc. 138, 13806–13809 (2016).

24. Yoshikai, N. & Nakamura, E. Mechanisms of nucleophilic organocopper(I) reactions. Chem. Rev. 112, 2339–2372 (2012).

25. Bartz, S. H. et al. Complexes of the Gilman reagent with double bonds across the π–π continuum. Organometallics 31, 7827–7838 (2012).

26. Bartz, S. H., Cope, S. K., Murphy, M., Ogle, C. A. & Taylor, B. J. Rapid injection NMR in mechanistic organocopper chemistry. Preparation of the elusive copper(III) intermediate. J. Am. Chem. Soc. 129, 7208–7209 (2007).

27. Haytertunyan, S. R., den Hartog, T., Georgs, K., Minnaard, A. J. & Feringa, B. L. Catalytic asymmetric conjugate addition and allylic alkylation with grignard reagents. Chem. Rev. 108, 2824–2852 (2008).

28. Alcxakis, A., Krause, N., Woodward, S. (eds.) Copper-Catalyzed Asymmetric Synthesis (Wiley-VCH, Weinheim, Germany, 2014).

29. Yamamoto, Y., Yamamoto, S., Yatagai, H., Ishihara, Y. & Maruyama, K. Lewis acid mediated reactions of organocopper reagents. Entrainment in the conjugate addition to alpha, beta-unsaturated ketones, esters, and acids via the RCu.cntdot.BF₃ system. J. Org. Chem. 47, 119–126 (1982).

30. Nakamura, E., Yamamako, M. & Mori, S. Complexation of Lewis acid with trialkylcupfer(III): on the origin of BF₃-acceleration of cuprate conjugate addition. J. Am. Chem. Soc. 122, 1826–1827 (2000).

31. Lipshutz, B. H., Ellsworth, E. L. & Dimock, S. H. On the composition of Yamamoto’s reagent: “RCu.cntdot.BF₃,” J. Am. Chem. Soc. 112, 5869–5871 (1990).

32. Corey, E. J. & Boaz, N. W. The reactions of combined organocuprate-chlorotrimethylsilane reagents with conjugated carbonyl compounds. Tetrahedron Lett. 26, 6019–6022 (1985).

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Author contributions

R.P.J. and F.L. designed and performed the experiments. T.P. performed additional experiments with respect to mechanistic studies. All authors contributed to editing the manuscript. S.R.H. guided the research.

Additional information

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