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Chiral amine–imine ligands based on *trans*-2,5-disubstituted pyrrolidines and their application in the palladium-catalyzed allylic alkylation

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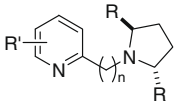
ABSTRACT

A series of amine–imine bidentate ligands based on a *trans*-2,5-disubstituted pyrrolidine and pyridine moieties have been prepared. The use of these ligands in the palladium-catalyzed allylic alkylation reaction of *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate is reported. The results suggest that these ligands are good catalyst precursors for the reaction. Electronic modification on the pyridine ring of the ligands does not have a significant effect on the enantioselectivity of the reaction but does on the reaction rate, while structural modification on either the pyridine or the pyrrolidine moiety affords dramatic changes on the outcome of the stereochemistry. Evidence from various studies suggested that during the palladium-catalyzed allylic alkylation reaction, nucleophilic attack onto the 1,3-diphenylallyl moiety in the transition state occurs mainly *trans* to the pyridine ring of the less stable conformation of the palladium complexes.

1. Introduction

Since its introduction by Whitesell in 1977, C_2-symmetric *trans*-2,5-disubstituted pyrrolidines[1] have played an important role as useful chiral auxiliaries in asymmetric synthesis.[1–13] Despite their great success as chiral auxiliaries in asymmetric reactions, incorporation of *trans*-2,5-disubstituted pyrrolidines in chiral ligands for transition metal-catalyzed asymmetric reactions is relatively rare.[14–20] We believe that the potential of this chiral building block to influence asymmetric transformations has not been fully investigated. As part of an ongoing project on the design and synthesis of ligands for asymmetric catalytic reactions, we developed a modular synthetic strategy for preparing amine–imine ligands based on *trans*-2,5-disubstituted pyrrolidines.[16] Since our initial report of this class of ligands,[16] several examples of both *trans*-2,5-disubstituted pyrrolidine-containing[20–26] and pyridine–amine[27–30] and ligands have been reported, in addition to many tertiary diamines.[31]

This type of ligand is constructed by linking a pyridine ring to the pyrrolidine ring as chiral bidentate ligands **A**. Nitrogen atoms from both the pyridine and pyrrolidine moieties are different electronically and are assumed to provide different binding properties to transition metals. Although pyridine is a strong electron-donating ligand, the delocalized π-system provides a tool for tuning the electronic nature of this moiety with substituents. While the different donor abilities of the pyridine and pyrrolidine rings can serve as an electronic differentiator for transition metal-catalyzed asymmetric reactions, the *trans*-2,5-disubstituted pyrrolidine moiety can provide a chiral influence for asymmetric discrimination on prochiral substrates.



A: n = 1, 2

To study the scope and efficiency of this new type of bidentate ligand, we modified the ligands in three ways: modification of the pyrrolidine ring to provide different chiral environments for asymmetric recognition; variation of the substituents on the pyridine ring to create different electronic properties for the ligands; and alteration of the linkage between the pyridine and the pyrrolidine rings to provide different chelation geometry for the catalysts. Herein we report in detail the synthesis and application of this series of pyridine–pyrrolidine ligands in the palladium-catalyzed allylic alkylation reaction of (*rac*)-(*E*)-1,3-diphenylprop-2-enyl acetate with dimethyl malonate.

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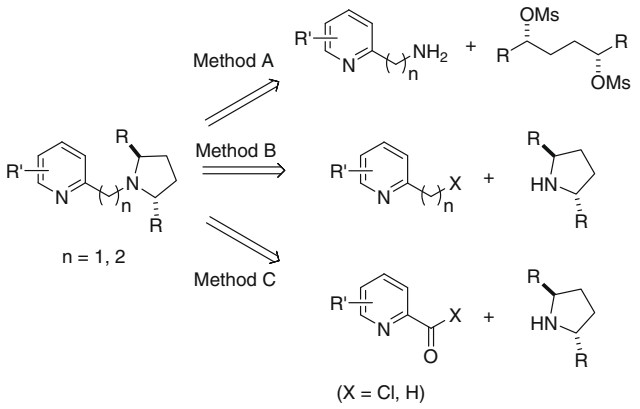
2. Results and discussion

2.1. Synthetic strategy

Retrosynthetic analysis reveals three different strategies for the construction of this series of new chiral ligands (Scheme 1). In the first route, a pyridine with a pendant amine is used to cyclize the dimesylate of a chiral 1,4-diol to form the desired ligands (method A). In the second route, a preformed *trans*-2,5-disubstituted pyrrolidine building block is allowed to react with a 2-halomethylpyridine (method B). In the third route, condensation of a *trans*-2,5-disubstituted pyrrolidine and a pyridinyl carboxylic acid or aldehyde followed by reduction forms the ligand (method C). All three methods rely on the asymmetric synthesis of chiral 1,4-diols since they are the precursors for the dimesylates of method A as well as the pyrrolidines of methods B and C.

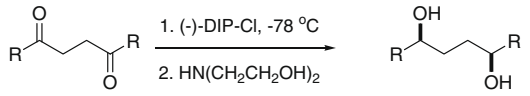


Scheme 1. Retrosynthetic analysis of ligand synthesis.

2.2. Synthesis of chiral 1,4-diols

Adopting a methodology developed by Masamune[32] and Chong,[33] the synthesis of *trans*-2,5-disubstituted pyrrolidine-containing ligands started with the preparation of a series of chiral 1,4-diols. These were generally prepared from the corresponding 1,4-diketones by asymmetric reductions. Commercially available 2,5-hexanedione was reduced to (+)-(2*S*,5*S*)-2,5-hexanediol by Baker's yeast using a slightly modified procedure reported by Lieser[34] and Haufe.[35] However, all other 1,4-diketones were 1,4-diaryl-1,4-butanediones that were prepared by reduction of the corresponding 1,4-diaryl-2-buten-1,4-diones, in turn were readily prepared in good yields using the Friedel–Crafts reaction.[36–40] Asymmetric reduction of the 1,4-diaryl-1,4-butanediones to the corresponding diols was achieved using (−)-DIP-Cl as the reducing agent,[33] originally developed by Brown et al. (Scheme 2).[41] Thus, diketones **1** and **2** were reduced selectively with (−)-DIP-Cl without difficulty to provide chiral diols **6** and **7** in high diastereo- and enantioselectivities. Diols **6** and **7** are colorless crystalline compounds that can be easily purified by recrystallization from CH_2Cl_2–hexanes. Diketone **3** was extremely difficult to reduce, with 3 equiv of (−)-DIP-Cl per carbonyl group needed to drive the reaction to completion. Although the selectivity was good (>99% ee, >98% de), the yield was poor (19%, Scheme 2). The major product isolated was 2,5-dinaphthyltetrahydrofuran, possibly formed via a carbocation intermediate.

Asymmetric reduction of diketones **4** and **5** proved not to be feasible using (−)-DIP-Cl. The attempted reduction of **4** gave a pink gel-like compound as the crude product after workup and the desired product could not be isolated. The reaction was carried out under strongly acidic conditions; a strong acid can promote the



1: R = *p*-Tol
2: R = 4-*t*-BuPh
3: R = 2-naphthyl
4: R = 4-OMePh
5: R = mesityl

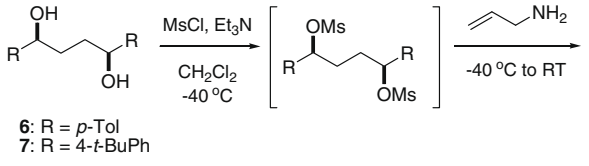
6: R = *p*-Tol, 83%
7: R = 4-*t*-BuPh, 85%
8: R = 2-naphthyl, 19%
9: R = 4-OMePh, decomposed
10: R = mesityl, no reaction

Scheme 2. Preparation of chiral 1,4-diaryl-1,4-diols.

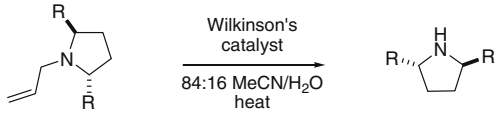
demethylation of the two methoxy groups to form the diphenol.[42] The phenol groups might be oxidized during the workup procedure. Diketone **5** was found to be resistant to common reducing reagents, including $LiAlH_4$, $NaBH_4$, and $LiBH_4$. Only starting material was recovered. MM2* calculations (Chem3D 2000) of the most stable conformation of **5** revealed that the phenyl groups were perpendicular to the plane of the adjacent carbonyl groups. This causes both faces of the carbonyl groups to be shielded by the 2,6-dimethyl groups on the phenyl rings, preventing the reducing agent from approaching.

2.3. Synthesis of pyrrolidines

Once the chiral diols were prepared, they were transformed into the corresponding dimesylates or pyrrolidines to use in method A or method B, respectively. Pyrrolidines **11**[32] and **12**[33] were prepared according to literature procedures. Chiral diols **6** and **7** were first transformed into their corresponding dimesylates. We found that the dimesylates of diols **6** and **7** are thermally labile and are decomposed at ambient temperature even in solution. Even at −20 °C, decomposition of the dimesylate of **6** in CH_2Cl_2 solution could be observed. Therefore, it was impossible to isolate these two dimesylates and characterize them spectroscopically. Instead, a procedure that maintains both dimesylates at low temperature and avoids total removal of solvent was used for the synthesis of ligands using these two intermediates. The addition of allylamine to the crude reaction mixture of the corresponding dimesylate afforded the cyclized products **13** and **14** (Scheme 3). Similar to the result reported by Chong,[33] a small amount of the *meso* diastereomer of the products was always observed, indicating a small degree of degradation of stereochemistry. However, the *rac* and *meso* diastereomers were easily separated by flash chromatography. The *N*-allyl-protected *trans*-2,5-diarylpyrrolidine **14** was transformed into the *trans*-2,5-diarylpyrrolidine **15** in 86% yield in the presence of Wilkinson's catalyst (Scheme 3). Due to the poor yield in the preparation of **13** (7%), a ligand containing *trans*-2,5-ditolylpyrrolidine was prepared using the direct cyclization reaction (Method A)



6: R = *p*-Tol
7: R = 4-*t*-BuPh

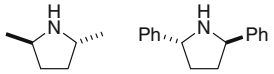


13: R = *p*-Tol, 7% from **6**
14: R = 4-*t*-BuPh, 35% from **7**

15: R = 4-*t*-BuPh, 86%

Scheme 3. Synthesis of *trans*-2,5-diarylpyrrolidine.

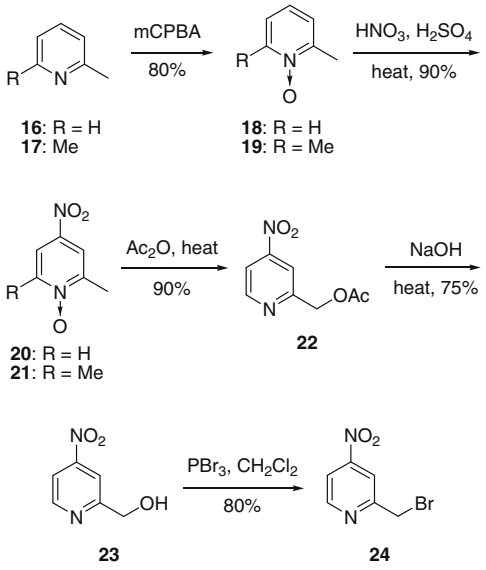
of the corresponding dimesylate with a pyridinylmethyl amine (vide infra).



11 **12**

2.4. Synthesis of pyridines

To utilize method B, 2-bromomethylpyridine moieties were needed to be prepared. 2-Picoline **16** and 2,6-dimethylpyridine **17** were oxidized (mCPBA) to afford the corresponding N-oxides **18** and **19**, respectively.[43] The N-oxides were then nitrated at the 4-position to give **20**[43] and **21**.[44] Subsequent transformation of **20** into an acetate by rearrangement in acetic anhydride at 100 °C[45] yielded **22** in 90% yield (Scheme 4). After hydrolysis, the hydroxymethyl pyridine **23** was further transformed to the desired bromide **24** by treatment with PBr_3. The nitro group at the 4-position of **20** and **21** can be easily transformed into an electron-donating group, such as a methoxy group, to afford **25**[45] and **26**[46] in quantitative yields (Scheme 5). After rearrangement in acetic anhydride, hydrolysis, and bromination with PBr_3, bromides **27** and **28** were obtained. Quinoline-based bromide **31**[47] was prepared from 2-quinolinecarboxylic acid **29** through esterification, reduction, and bromination (Scheme 6).

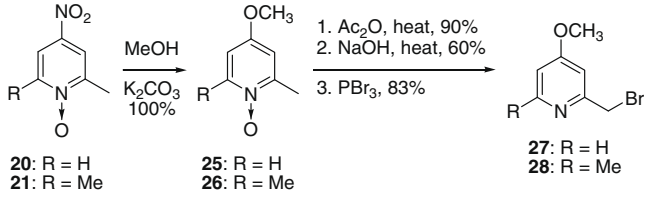


Scheme 4. Synthesis of 2-bromomethyl-4-nitropyridine.

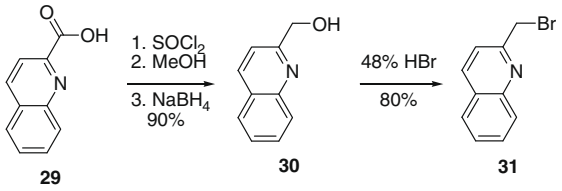
At ambient temperature, bromides **27** and **28**, which bear an electron-donating methoxy group at the 4-position of the pyridine ring, rapidly undergo self-condensation to form yellow solids that are insoluble in common organic solvents but are soluble in water. Fortunately, decomposition of the bromides can be avoided when the compounds are kept in solution. Thus, a procedure was developed to avoid the isolation of the bromides. For this reason, these intermediate bromides were used without purification.

2.5. Synthesis of ligands

Eleven chiral pyridine–pyrrolidine ligands have been prepared (Chart 3). Ligands **32** and **33** are constructed with *trans*-2,5-dimethylpyrrolidine **11**, and they differ in the length of the linkage between the pyridine and the pyrrolidine moieties. All other ligands are constructed with *trans*-2,5-diarylpyrrolidines. Ligands

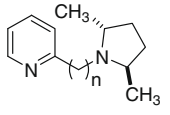


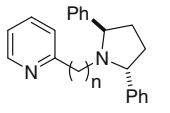
Scheme 5. Synthesis of 2-bromomethyl-4-methoxypyridine and 2-bromomethyl-4-methoxy-6-methylpyridine.

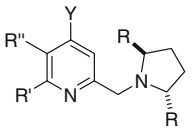


Scheme 6. Synthesis of 2-bromomethylquinoline.

34–**40** all contain a *trans*-2,5-diphenylpyrrolidine moiety, but are differentiated by substituents on the pyridine ring or by the lengths of the linkage between the pyridine and pyrrolidine moieties. Ligands **41** and **42** have remote modification on the *para*-position of the phenyl ring of the pyrrolidine moiety.





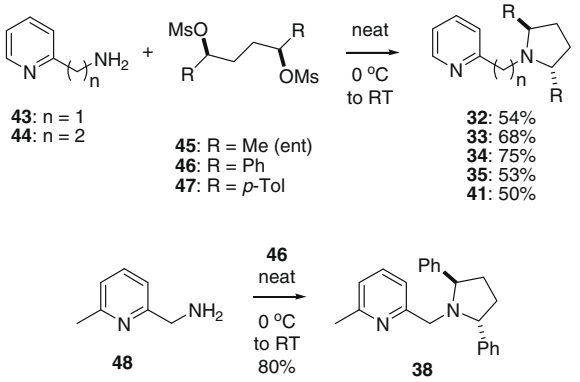


	R	R'	R''	Y
36:	Ph	H	H	NO_2
37:	Ph	H	H	OCH_3
38:	Ph	CH_3	H	H
39:	Ph	CH_3	H	OCH_3
40:	Ph	benzo		H
41:	*p*-Tol	H	H	H
42:	*p*-*t*BuPh	H	H	H

Both methods A and B worked satisfactorily to prepare the ligands. However, we encountered a difficulty in using method C. In the case of using *trans*-2,5-diphenylpyrrolidine to construct new ligands using method C with an acyl chloride, the first step proceeded well to form the amide in high yield. However, reduction of the amide using $LiAlH_4$ or $NaBH_4$ did not occur. For this reason, only the first two strategies were applied throughout the remainder of this study.

Ligands **32**–**35** were prepared according to method A (Scheme 7).[16] Ligand **41**, which is remotely modified on the two phenyl rings on the pyrrolidine ring, was also prepared by method A. Ligand **38** was prepared either by direct cyclization (method A), or by the coupling of *trans*-2,5-diphenylpyrrolidine with 6-methylpyridinylmethyl bromide (method B, vide infra). All the other ligands are prepared by method B.

The syntheses of **32**–**34** proceeded without significant epimerization.[16] There was also no detected erosion of stereochemistry for the synthesis of ligand **35**. However, degradation of stereochemistry was observed in the preparation of ligands **38** and **41** by direct cyclization (method A). Following the same procedure for the preparation of **34**,[16] synthesis of **38** gave a product, after column chromatography, with a de of 76% (^{1}H NMR), while synthesis of **41** afforded only a mixture with a de of about 50% (determined by ^{1}H NMR). Fortunately, only after one recrystallization



Scheme 7. Synthesis of chiral pyridine–pyrrolidine ligands by method A.

from hexanes, the de and ee of **38** increased to >99% (by chiral HPLC). Similarly, only one recrystallization of **41** from hexanes brought the de to >98% and ee to >99%. The constitution and configuration of **41** was confirmed by X-ray structure analysis (Fig. 1), and therefore also confirmed the absolute configuration of the corresponding chiral diol **4**. It is unlikely that epimerization occurs during the mesylation step in the conversion of chiral alcohol 1,4-diphenyl-1,4-butanediol to the corresponding dimesylate **46**, since previously isolated samples of this intermediate showed little to no degradation in diastereomeric purity. Furthermore, cyclization of **46** with 2-(aminomethyl)pyridine, leading to ligand **34**, proceeded with little epimerization.

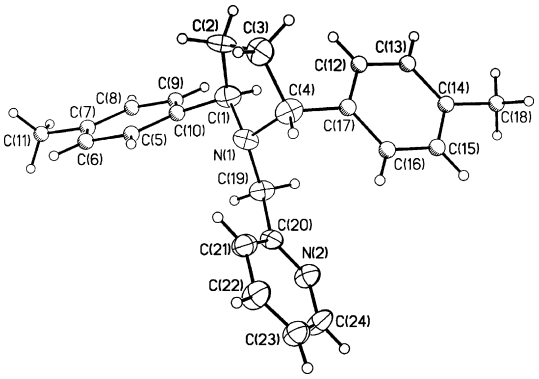


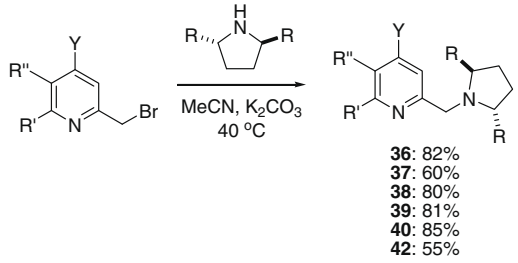
Figure 1. ORTEP diagram of ligand **41** showing atom labeling scheme. Thermal ellipsoids at 30% probability.

Method B was used to prepare ligands **36**–**40** and **42** (Scheme 8). A bromomethylpyridine and a pyrrolidine were allowed to react in acetonitrile or acetone at 40 °C in the presence of K_2CO_3 to form the corresponding pyridine–pyrrolidine ligand in good yield. Since this method does not involve any reaction on the stereogenic centers, we did not observe any degradation of the pre-established stereochemistry. In this respect, method B has the advantage over method A for the synthesis of these ligands.

2.6. Catalytic results for palladium-catalyzed allylic alkylation

Upon preparation of these pyridine–pyrrolidine ligands, we sought to test them in transition metal-catalyzed asymmetric reactions. We applied these ligands in the palladium-catalyzed allylic alkylation reaction of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate as a nucleophile (Table 1).

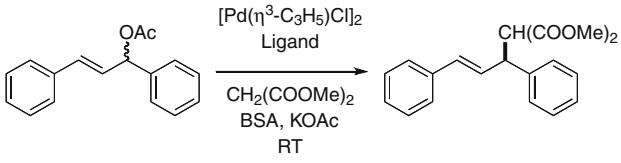
The effect of solvent on the reaction was first tested using ligand **32** in the presence of BSA and a catalytic amount of potassium acetate. Chlorinated solvents resulted in higher yields. In



Scheme 8. Synthesis of chiral pyridine–pyrrolidine ligands by method B.

toluene, the reaction required 70 h to achieve total conversion with an isolated yield of only 30%. The enantioselectivity was also poor in non-polar solvents. Acetonitrile provided somewhat better enantioselectivity for the reaction, but the yield was below 50%. Dichloromethane appeared to be the solvent of choice for this reaction. When the reaction was carried out in CH_2Cl_2, it proceeded in 69% yield with comparable enantioselectivity (Table 1, entries 1–3). Therefore, most reactions carried out thereafter were in CH_2Cl_2.

Table 1
Palladium-catalyzed allylic alkylation of *(rac)-(E)*-1,3-diphenylprop-2-enyl acetate



No.	Ligand[a]	Solvent	Time (h)	Yield (%)	%ee[b]	Config.[c]
1	**32**	CH_2Cl_2	28	69	21	(*S*)
2	**32**	MeCN	23	46	27	(*S*)
3	**32**	Tol.	70	30	20	(*S*)
4	**33**	CH_2Cl_2	71	43	17	(*R*)
5	**33**	Toluene	238	11	12	(*R*)
6	**34**	CH_2Cl_2	9	100	62	(*R*)
7[d]	**34**	THF	185	85	53	(*R*)
8[d,e]	**34**	THF	185	30	46	(*R*)
9	**35**	CH_2Cl_2	168	0	—	—
10	**36**	CH_2Cl_2	240	100	63	(*R*)
11	**37**	CH_2Cl_2	11	100	64	(*R*)
12	**38**	CH_2Cl_2	21	83	35	(*S*)
13[e]	**38**	CH_2Cl_2	100	85	33	(*S*)
14	**39**	CH_2Cl_2	20	100	40	(*S*)
15	**40**	CH_2Cl_2	115	60	20	(*S*)
16	**41**	CH_2Cl_2	10	100	70	(*R*)
17[e]	**41**	CH_2Cl_2	26	100	70	(*R*)
18	**42**	CH_2Cl_2	10	100	68	(*R*)

[a] All reactions were run using 10 mol % of ligand and 2.5 mol % of Pd source except as indicated.
[b] The percentage ee was determined by ^1H NMR ($CDCl_3$) using the shift reagents $Pr(tfc)_3$ or $Eu(hfc)_3$.
[c] Determined by comparison of the specific rotation with the literature values.
[d] NaH was used as the base instead of BSA + KOAc.
[e] These reactions were run using 5 mol % of the ligands and 1.2 mol % of Pd source.

Several trends have been identified from the results shown in Table 1. First, the *trans*-2,5-diarylpyrrolidine moiety provides better stereoselectivity in this catalytic system than the dimethyl analogues. When 10 mol % of ligand and 2.5 mol % of palladium source were used in combination with BSA as the base, *trans*-2,5-diphenylpyrrolidine-containing ligand **34** catalyzed this reaction to completion in less than 10 h, affording 100% isolated yield with an ee of 62% (Table 1, entry 6), while the structurally similar *trans*-2,5-dimethylpyrrolidine analogue only catalyzed this reaction to afford up to 69% yield (Table 1, entry 1) and up to 27% ee (Table 1, entry 2). When the base was changed to NaH, and the solvent to THF, the

time of the reaction catalyzed by the palladium complex of **34** was greatly increased while the stereoselectivity was decreased, resulting in a yield of only 85% after 185 h and an ee of only 53% (Table 1, entry 7). When the loading of the catalyst was decreased, both the yield and ee for the reaction involving **34** as catalyst precursor were decreased, affording a yield of only 30% in 185 h and an ee of 46% (Table 1, entry 8). The other *trans*-2,5-diarylpyrrolidine-containing ligands also provided better yields and selectivities for this reaction than the dimethyl analogues.

Changing the length of the linkage between the pyridine moiety and the pyrrolidine moiety resulted in the stereoselectivity of the reaction being reversed and the activity of the catalyst being decreased. For example, a palladium complex of ligand **32** catalyzed the allylic alkylation reaction in CH_2Cl_2 to afford the product in 21% ee with the major product with an (*S*)-configuration (Table 1, entry 1). Ligand **33**, which differs from **32** by an ethylene bridge rather than a methylene bridge between the pyridine and the pyrrolidine moieties, afforded the (*R*)-isomer as the major product with a lower ee and a lower yield (Table 1, entry 4). This reaction also required a much longer time for completion (Table 1, entry 4 vs entry 1, entry 5 vs entry 3). When the ligands contain a *trans*-2,5-diarylpyrrolidine moiety, increasing the length of the bridge greatly decreased the reactivity of the ligand, resulting in no detectable product after running the reaction in order for one week (Table 1, entry 9 vs entry 6). These results suggest that for better selectivity and reactivity in this catalytic system, the ligand–metal complex must have a five-membered rather than a six-membered chelate ring. A similar inversion of enantioselectivity with a longer bridge was reported for pyridine–aziridine ligands.[29]

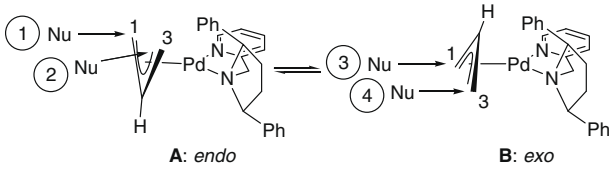
It was found that modification on the 6-position of the pyridine ring caused reversal of the stereoselectivity for the allylic alkylation, similar to an increase in the chelate size. Ligand **34** catalyzed the reaction to afford the major product as the (*R*)-enantiomer. However, ligand **38,** which only differs from **34** in that it has a methyl group on the 6-position of the pyridine ring, catalyzed the reaction with the opposite stereoselectivity, giving the (*S*)-enantiomer as the major product (Table 1, entries 12 and 13). The same phenomenon was also observed when ligands **39** and **40** were used in the catalytic reaction (Table 1, entries 14 and 15). A similar inversion of enantioselectivity with a C6-pyridine substituent was reported for pyridine–aziridine ligands.[29]

Changing the electronic properties of the substituents on the 4-position of the pyridine ring has no significant effect on the stereoselectivity of the reaction. Instead, the electronic properties of the substituents on this position only affected the reactivity of these ligands. We found that electronically deficient ligands had a much lower reactivity than those of the electronically rich ones. Ligands **34**, **36**, and **37** afforded essentially the same selectivity for the catalytic reaction. However, the reaction times were quite different. The reaction catalyzed by **34** was completed in about 9 h with an ee of 62% (Table 1, entry 6). With an electron-donating methoxy group at the 4-position of the pyridine ring, ligand **37** also catalyzed the allylic alkylation to completion in approximately the same time with similar selectivity (Table 1, entry 11). However, ligand **36**, which has a strong electron-withdrawing group on the 4-position of the pyridine ring, catalyzed the reaction to completion in 240 h (Table 1, entry 10). Ligands **38** and **39,** which only differ from each other by an additional methoxy group at the 4-position of the pyridine ring, gave comparable selectivities and reactivities (Table 1, entries 12 and 14).

Remote modification of the pyrrolidine ring provided enhanced selectivity and reactivity. Ligands **41** and **42** exhibited a moderate improvement over ligand **34** and are the most promising ligands in this series to date. When *trans*-2,5-ditolylpyrrolidine-containing ligand **41** was used as a catalyst precursor, the reaction gave the (*R*)-enantiomer as the major product in 70% ee and quantitative yield within 10 h (Table 1, entry 16). Lowering the catalyst loading to half only resulted in a longer reaction time, but the enantioselectivity remained the same (Table 1, entry 17). Using the sterically bulkier *trans*-2,5-bis(4-*tert*-butylphenyl)pyrrolidine moiety in ligand **42** did not provide better selectivity, but the reactivity remained unchanged (Table 1, entry 18).

2.7. Structural studies of the η3−allyl palladium ligand complexes

In an attempt to better understand the role of these ligands in the palladium-catalyzed allylic alkylation reaction and to help optimize the system, consideration of the structures of the η^3-allyl palladium ligand complexes was appropriate. For a C_2-symmetric ligand and a mirror symmetric allyl group, the η^3-allyl metal ligand complex has only one single configuration. Therefore the stereoselectivity of the reaction depends solely on the regioselectivity of the nucleophilic attack on the η^3-allyl moiety.[48] However, when the ligand lacks C_2-symmetry, the configuration of the η^3-allyl group (*endo* or *exo*) makes a difference. Complexes **A** and **B** differ in the configuration of the η^3-allyl moiety (Scheme 9). In this system, nucleophilic attack can occur at any of the 4 allylic termini. For the reaction to exhibit stereoselectivity, there should not only be discrimination between the two configurations of the complex at the transition state, but also a bias between the reactivity of C1 and C3. The allyl carbon *trans* to pyrrolidine will be commonly referred to as C1, and that *trans* to pyridine as C3. Hence, an ideal ligand directs nucleophilic attack to only one of the four positions.



Scheme 9. Possible nucleophilic attacks on the η^3-allyl palladium ligand complexes of non-C_2-symmetric ligand **34**.

A previously obtained crystal structure of the allyl palladium complex of **32** exhibited a disordered allyl group.[16] This strongly suggests that *trans*-2,5-dimethylpyrrolidine is not effective at restricting the conformation of the allyl group. We have obtained an X-ray structure of the allyl palladium complex of ligand **34** (**49**, Fig. 2). Ligand **34** was allowed to react with the allyl palladium chloride dimer and $NaClO_4$ to form the complex. The crystals of the complex were grown from CH_2Cl_2–ether solution. The diastereomer with the allyl group at the *endo* position was found in the crystal. One of the phenyl groups of the pyrrolidine moiety masks the allyl C3 position from the top face. As expected, the structure shows a bias for the two Pd–C bonds. Pd–C3 is longer than Pd–C1 by about 0.03 Å. This suggests that the atom trans to C3 is a better π-acceptor (pyridine sp^2-nitrogen). The pyridine sp^2-nitrogen is softer than the sp^3-nitrogen, and therefore provides a stronger '*trans*-influence'.[49] That the Pd–C3 bond is longer than the Pd–C1 bond also suggests that the Pd–C3 bond is weaker and should be broken more easily than Pd–C1 bond when subjected to nucleophilic attack.[48] Based on the discussion above, we believed that the nucleophilic addition on the allyl group is more likely to happen at the C3 position (*trans* to pyridine) in this system.

2.8. Molecular mechanics (MM3*) study of the η^3-allyl palladium complexes

Understanding the origin of the stereoselectivity of the catalytic processes can aid the optimization of the ligands for better

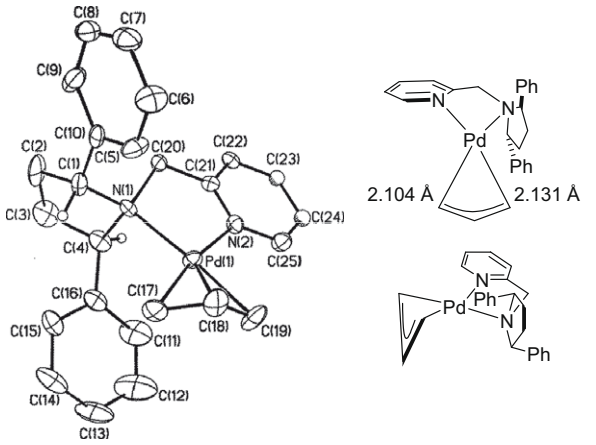


Figure 2. (l.) ORTEP diagram of [(η^3-allyl)·Pd·**34**]$^+ClO_4^-$ **49** with thermal ellipsoids at 30% probability. The perchlorate counterion and the hydrogen atoms, except for those bonded to the chiral carbon atoms, are omitted for clarity. (r.) Two alternate views of **49**.

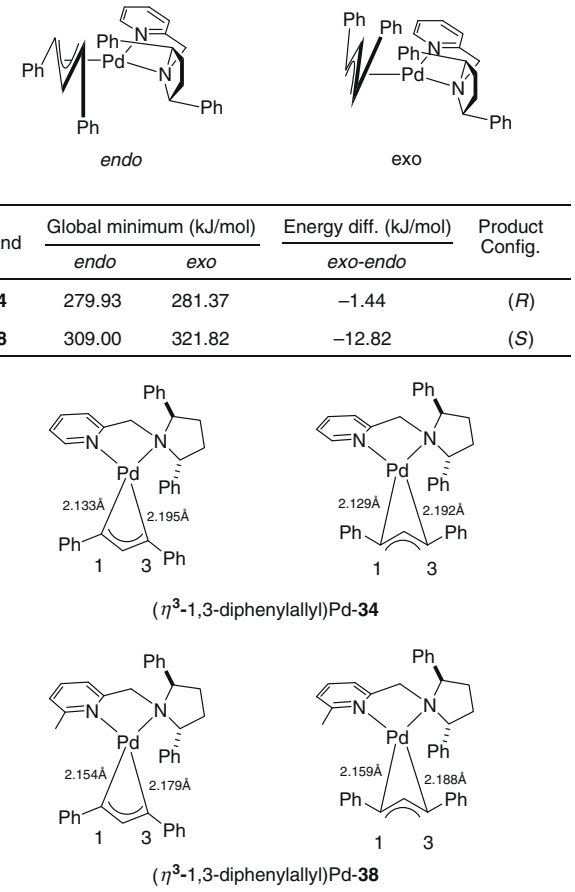
selectivity and activity. We used computational chemistry to obtain energy-minimized structures of the η^3-1,3-diphenylallyl Pd complexes of ligands **34** and **38** using Norrby's parameters for the MM3* force field for palladium-catalyzed allylic alkylation (MacroModel 6.0).[50–52] To facilitate finding global minimum structures, the calculation was divided into two subsets, one with the η^3-1,3-diphenylallyl moiety having an *endo* configuration and one with the *exo* configuration. Monte Carlo conformational searches were performed to find multiple conformations of the two configurations of each complex and then the respective global minima. The calculated energies for the global minimum of both *endo* and *exo* configurations were compared, giving quantitative results of which diastereomer was predicted to be more abundant (Fig. 3). Monte Carlo searches found multiple conformations for both configurations of each η^3-1,3-diphenylallyl Pd complex, indicating the flexibility of the pyrrolidine ring. Since ligand flexibility can decrease the stereoselectivity of the catalytic reactions by increasing the number of accessible transition states, the flexibility of the pyrrolidine ring may be responsible for the moderate stereoselectivity exhibited by these pyridine–pyrrolidine ligands.[26]

The calculated distance between the palladium and the allyl terminus *trans* to the pyridine ring was consistently longer than that between the palladium and the allyl terminus *trans* to the pyrrolidine ring (Fig. 3). This supports our assumption based on the *trans* influence. Since the pyridine nitrogen is also a π-acceptor, it weakens the Pd–C bond *trans* to it. This allows the Pd–C bond to be broken more easily. Koga[48] and Pfaltz[53] in separate studies obtained evidence that the allyl terminus with a longer Pd–C bond possessed more positive charge and therefore was more readily attacked by nucleophiles.

2.9. Mechanistic consideration for the palladium-catalyzed allylic alkylation reaction

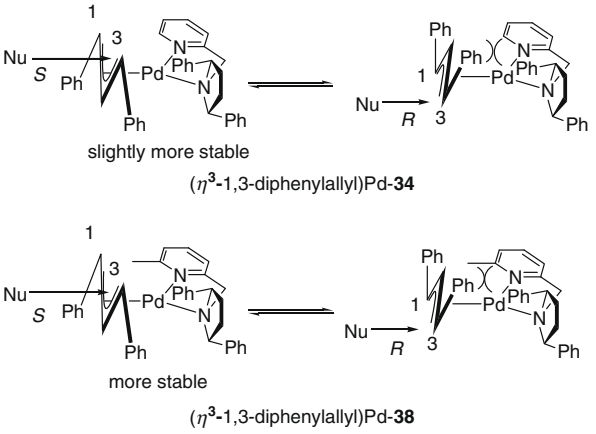
Since the major product from both catalysts [(*R*) for **34** and (*S*) for **38**] is known, a brief discussion regarding the origin of the stereoselectivity is possible. If the nucleophilic attack always occurs *trans* to the pyrrolidine nitrogen, then in the case of **34**, attack occurs at the more stable *endo* diastereomer, while in the case of **38**, the attack occurs at the less stable *exo* diastereomer to provide the observed stereoselectivity. This is unlikely to be true. If an attack always occurs *trans* to the pyridine nitrogen on the more stable diastereomer, then the selectivity for ligand **38** should be better than that for **34**. Taking into account that **38** only provided 33% ee, while **34** provided up to 65% ee, this is also not likely to be the case. If an attack always occurs at the major ground state diastereomer at the same position (i.e., *trans* to the pyridine or pyrrolidine nitrogen), both should form the same major product. This prediction then conflicts with our experimental data [**34** gave (*R*) and **38** gave (*S*)].

We propose that nucleophilic attack occurs mainly at the less stable *exo* diastereomer at the terminus *trans* to the pyridine rings (C3, Scheme 10). The less stable diastereomers (*exo*) are more reactive toward nucleophilic attack since their energies are higher than the more stable diastereomers (*endo*). In the case of ligand **34**, the difference between the two Pd–C bonds is large (~0.06 Å) hence we can consider the carbon *trans* to the pyridine nitrogen (sp^2)



ligand	Global minimum (kJ/mol)		Energy diff. (kJ/mol)	Product Config.
	endo	*exo*	*exo-endo*	
34	279.93	281.37	–1.44	(*R*)
38	309.00	321.82	–12.82	(*S*)

Figure 3. Calculated Pd–C bond lengths for the complexes of ligands **34** and **38**.



Scheme 10. Proposed mechanism for the palladium-catalyzed allylic alkylation.

bearing more positive charge than the carbon *trans* to the pyrrolidine nitrogen (sp^3), and therefore is more subject to nucleophilic attack.[48,53] Because in the ground state the complex of ligand **34** exists in about a 1:1 ratio for its two configurations (based on ^1H NMR studies not shown), the selectivity results mainly from the electronic difference between the two allylic termini.

In the case of ligand **38**, the distance between the two Pd–C bonds is much smaller (0.02–0.03 Å). The difference of the electronic properties of both allylic termini still favors nucleophilic attack on the carbon *trans* to the pyridine nitrogen. However, since the major diastereomer (*endo*) is much more stable than the minor diastereomer (*exo*, favored by 12.82 kJ/mol), the *endo* diastereomer is more abundant than the *exo* diastereomer in solution (^1H NMR studies). Nucleophilic attack on the more abundant *endo* diastereomer at the allylic terminus *trans* to the pyridine nitrogen contributes to the formation of the (*S*)-enantiomer of the product. The less effective results (35% ee) and the opposite selectivity (*S* vs *R*) obtained from the reaction involving ligand **38** result from the competition of the aforementioned two reaction routes. However, it is difficult to rule out other possibilities for the origin of stereoselectivity, including the involvement of *syn–anti* allyl isomers, as well as the unfavorable steric interaction between developing product and the pyridine methyl group **38** in a late transition state,[54] at this time.

3. Conclusions

In conclusion, we have successfully prepared a novel type of chiral bidentate ligands based on *trans*-2,5-disubstituted pyrrolidine building blocks. These ligands are effective catalyst precursors for the palladium-catalyzed allylic alkylation and provide moderate to good stereoselectivity. The stereoselectivity of this reaction catalyzed by the palladium complexes of the pyridine–pyrrolidine ligands could be adjusted by changing the substituent at the 6-position of the pyridine ring, or the substituents at the pyrrolidine ring as well as the chelate size of the complexes. MM3* calculations, in concert with the catalytic results, suggest that nucleophilic attack on the η^3-1,3-diphenylallyl moiety predominantly occurred *trans* to the pyridine ring at the less stable configuration in the transition state, although other possibilities have not been ruled out.[55]

4. Experimental

4.1. General methods

All reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere using oven-dried glassware. THF was either distilled from Na or dried over freshly activated 4 Å molecular sieves. CH_2Cl_2 was either distilled from CaH_2 or dried over freshly activated 4 Å molecular sieves. Toluene was distilled from Na. Pyridine and methanol were dried over freshly activated 4 Å molecular sieves before use. Compounds **11**,[32] **12**,[33] **18–20**,[43] **21**,[44] **25**,[45] **26**,[46] and **32–34**[16] were prepared according to literature procedures. All other solvents and reagents were purchased from commercial sources and used as received. NMR spectra were recorded in $CDCl_3$ solution with the solvent peaks (^1H 7.24 ppm or ^{13}C 77.0 ppm) as internal standards. Melting points were not corrected.

4.2. Synthesis of butandiols

4.2.1. (−)-(1*S*,4*S*)-1,4-Di(4-methylphenyl)-1,4-butandiol 6

Freshly distilled THF (35 mL) was added to a mixture of 1,4-bis(4-methylphenyl)-1,4-butandione **1** (1.20 g, 4.50 mmol) and (−)-DIP-Cl (4.18 g, 13.0 mmol) at −78 °C under N_2. The mixture was stirred at −78 °C for 2 h and then allowed to warm to rt over a 24-h period. The solvent was removed in vacuo, and the residue was stirred at 40 °C in vacuo (0.3 torr) for 24 h. The residue was dissolved in dry ether (50 mL) and cooled to 0 °C, and diethanolamine (2.30 g, 21.9 mmol) was added. The mixture was stirred vigorously at 0 °C for 30 min and at rt for 24 h. The resulting white precipitate was removed by filtration through a pad of Celite. Solvent was removed in vacuo and the residue was dissolved in hexane (30 mL) and stored in a freezer overnight. The colorless precipitate was collected by filtration and recrystallized from hexanes–CH_2Cl_2 to afford **6** as a colorless solid (1.01 g in two crops, 83%). This product can be used directly in the next step. For analytical purpose, a small portion of this product was further purified by recrystallization in hexane–ethanol to afford the product as colorless needles: ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.1 Hz, 4H), 7.12 (d, J = 8.1 Hz, 4H), 4.66 (t, J = 5.6 Hz, 2H), 2.41 (br s, 2H), 2.32 (s, 6H), 2.19–1.87 (m, 4H), 1.80–1.73 (m 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 138.0, 130.0, 126.7, 75.3, 36.8, 22.0; $[\alpha]_D^{25} = -47.0$ (c 0.65, CH_2Cl_2); mp = 118–119 °C; MS (FAB$^+$) m/z (rel intensity) 253 ([MH−H_2O]$^+$, 100), 235 (52), 185 (92), 137 (38), 93 (97); exact mass (FAB$^-$) m/z calcd for $C_{18}H_{21}O_2$ ([M−H]$^-$) 269.1542, found 269.1548; ee = 99.5%, de = 98.0% [Chiralcel OD, 99.5:0.5 hexanes/ethanol, 0.5 mL/min, 65.4 min (*S*,*S*), 67.6 min (*meso*), 70.3 min (*R*,*R*)]. Anal. Calcd for $C_{18}H_{22}O_2$ (270.2): C, 79.96, H, 8.20. Found: C, 79.74, H, 8.17.

4.2.2. (−)-(1*S*,4*S*)-1,4-Di(4-*tert*-butylphenyl)-1,4-butandiol 7

Freshly distilled THF (160 mL) was added to a mixture of 1,4-bis(4-*tert*-butylphenyl)-1,4-butandione (**2**, 8.00 g, 23 mmol) and (−)-DIP-Cl (16.00 g, 50.0 mmol) at −78 °C under N_2. The mixture was stirred at −78 °C for 2 h and then allowed to warm to rt over a 24-h period. The solvent was removed in vacuo, and the residue was stirred at 40 °C in vacuo (0.3 Torr) for 24 h. The residue was dissolved in dry ether (350 mL) and cooled to 0 °C, and diethanolamine (8.00 g, 76 mmol) was added. The mixture was stirred vigorously at 0 °C for 30 min and at rt for 24 h. The resulting white precipitate was removed by filtration through a pad of Celite. The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO_2, hexanes/ether = 1:1) to afford **7** as a colorless solid (5.02 g, 63%). ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (d, J = 6.5 Hz, 4H), 7.25 (d, J = 6.5 Hz, 4H), 4.66 (m, 2H), 2.77 (broad, 2H), 1.88 (m, 4H), 1.30 (s, 18H); C NMR (62.896 MHz, $CDCl_3$) δ 150.4, 141.6, 125.6, 125.3, 74.4, 35.8, 34.5, 31.3; $[\alpha]_D^{25} = -31.3$ (c 1.14, CH_2Cl_2); mp = 138–139 °C; MS (FAB$^+$) m/z (rel intensity) 709.6 ([2M+H]$^+$, 15), 335.3 (60), 263.2 (43), 207.2 (32), 185.1 (100), 93.2 (82), 57.4 (51); exact mass (FAB$^-$) m/z calcd for $C_{24}H_{33}O_2$ ([M−H]$^-$) 353.2481, found 353.2477; ee >95%, de >95% (^1H NMR, Mosher's acid as chiral-shifting agent, no signal for the stereoisomers could be found). Anal. Calcd for $C_{24}H_{34}O_2$ (354.3): C, 81.31, H, 9.67. Found: C, 81.02, H, 9.60

4.2.3. (−)-(1*S*,4*S*)-1,4-Di(naphth-1-yl)-1,4-butandiol 8

Freshly distilled THF (20 mL) was slowly added to a mixture of 1,4-bis(1-naphthyl)-1,4-butandione (**3**, 0.2791 g, 0.80 mmol) and (−)-DIP-Cl (2.5828 g, 8.1 mmol) at −78 °C. The solution was stirred for 2 h at −78 °C and then for 12 h at rt. The solvent was removed in vacuo and the residue was stirred in vacuo (0.1 Torr) at 40 °C for 24 h. Dry THF (20 mL) and diethanolamine (0.97 g, 16 mmol) were then added at 0 °C and the mixture was stirred vigorously for 30 min at 0 °C and for 12 h at rt. After workup, a viscous oil was obtained. Purification by flash chromatography (SiO_2, hexane/ether = 1:1) afforded **8** as colorless crystals. (50.5 mg, 19%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.82 (t, J = 3.5 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 7.1 Hz, 2H), 7.49–7.43 (m, 6H), 5.56 (s, 2H), 2.90 (d, J = 18.8 Hz, 2H), 2.23–

2.21 (m, 2H), 2.16–2.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 134.7, 131.2, 129.8, 128.8, 126.9, 126.4, 126.3, 123.9, 123.6, 72.2, 36.1; mp 145–147 °C; $[\alpha]_D^{25} = -68.0$ (*c* 1.1, CH_2Cl_2); ee = 99.3%, de = 99.4% [Chiralcel OD, 90:10 hexanes/ethanol, 1 mL/min, 7.1 min (*S*,*S*), 13.3 min (*meso*), 21.9 min (*R*,*R*)]. Anal. Calcd for $C_{24}H_{22}O_2$ (270.2): C, 84.18, H, 6.48. Found: C, 84.14, H, 6.44.

4.3. Synthesis of pyrrolidines

4.3.1. (+)-(2*R*,5*R*)-1-Allyl-2,5-di-(4-*tert*-butylphenyl)pyrrolidine 14

To a cold solution (−78 °C) of methanesulfonyl chloride (2.0 mL, 27 mmol) in CH_2Cl_2 (100 mL) was added a solution of **5** (3.04 g, 8.6 mmol) and triethylamine (4.1 mL, 30 mmol) in CH_2Cl_2 (100 mL). The solution was stirred at −78 °C for 2 h and allylamine (60 mL) was added. The mixture was allowed to gradually warm to rt and stirred for 2 d. The mixture was concentrated in vacuo, and the residue was diluted with ether (300 mL), washed with satd $NaHCO_3$ (2 × 30 mL), brine (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to afford a yellow oil. Purification of this oil by flash chromatography (SiO_2, hexanes/ether = 30:1) afforded **14** as a colorless solid (1.50 g, 47%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 6.6 Hz, 4H), 7.25 (d, *J* = 6.6 Hz, 4H), 5.67 (m, 2H), 4.94 (m, 2H), 4.28 (t, *J* = 4.8 Hz, 2H), 2.96 (ddt, *J* = 1.8, 7.2, 18.0 Hz, 1H), 2.66 (dd, *J* = 7.2, 18.0 Hz, 1H), 2.48 (m, 2H), 1.90 (m, 2H), 1.32 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 140.9, 137.1, 127.6, 124.9, 115.4, 65.0, 49.8, 34.4, 33.1, 31.4; mp 57–59 °C; $[\alpha]_D^{25} = +111.5$ (*c* 1.1, CH_2Cl_2); MS (FAB$^+$) *m/z* (rel intensity) 376.3 (MH^+, 63), 246.1 (11). 185.1 (100), 93.2 (83); exact mass (FAB$^+$) *m/z* calcd for $C_{27}H_{38}N$ (MH^+) 376.3004, found 376.2997. Anal. Calcd for $C_{27}H_{37}N$ (375.3): C, 86.34, H, 9.93, N, 3.73. Found: C, 86.30, H, 9.89, N, 3.70.

4.3.2. (+)-(2*R*,5*R*)-2,5-Di-(4-*tert*-butylphenyl)pyrrolidine 15

(+)-(2*R*,5*R*)-1-Allyl-2,5-di-(4-*tert*-butylphenyl)pyrrolidine (**14**, 1.00 g, 2.7 mmol), $(Ph_3P)_3RhCl$ (Wilkinson's catalyst, 0.150 g, 0.174 mmol), and 100 mL of 84:16 acetonitrile/water mixture were placed in a 200-mL round-bottomed flask. The flask was evacuated and charged with argon three times, and then heated at reflux for 3 h before it was allowed to cool to rt. The mixture was diluted with ether (200 mL), the organic layer was separated and washed with brine (2 × 50 mL). The combined aqueous layers were back-extracted with ether (50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford a yellow solid. Purification of the crude product by flash chromatography (SiO_2, hexanes/ether = 1:1) afforded **15** as an off-white solid (0.767 g, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 4H), 7.33 (d, *J* = 8.5 Hz, 4H), 4.51 (t, *J* = 7.0 Hz, 2H), 2.37 (m, 4H), 1.96 (br s, 1H), 1.91 (m, 4H), 1.34 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 142.9, 126.0, 125.3, 61.8, 35.4, 34.4, 31.4; mp 122–123 °C; $[\alpha]_D^{25} = +106.5$ (*c* 1.13, CH_2Cl_2); MS (FAB$^+$) *m/z* (rel intensity) 336.3 (MH^+, 22), 246.1 (12). 185.1 (100), 93.2 (67); exact mass (FAB$^+$) *m/z* calcd for $C_{24}H_{34}N$ (MH^+) 336.2691, found 336.2691; ee >99%, de >99% [Chiralcel OD, 99:1:0.1 hexanes/ethanol/triethylamine, 1 mL/min, 15.6 min (*R*,*R*), 16.0 min (*meso*), 16.5 min (*S*,*S*)]. Anal. Calcd for $C_{24}H_{33}N$ (375.3): C, 85.91, H, 9.91, N, 4.17. Found: C, 85.80, H, 9.89, N, 4.09).

4.4. Synthesis of pyridines

4.4.1. 2-Acetoxymethyl-4-nitropyridine 22[43]

4-Nitro-2-picoline-N-oxide (**20**, 8.1 g, 58 mmol) was added to hot (100 °C) acetic anhydride (30 mL) over a period of 3 min. The mixture was maintained at 100 °C for 1 h until gas evolution ceased. Ethanol (30 mL) was then cautiously added and the mixture was allowed to reflux for 10 min. After the mixture was cooled to rt, it was poured into crushed ice (200 g) and the resulting mixture was neutralized with 4 M NaOH and extracted with chloroform (3 × 50 mL). The combined chloroform layer was washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo to afford a light brown oil. Flash chromatography (SiO_2, hexane/ether = 1:1) of the oil afforded **22** as an orange oil (10.2 g, 90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J* = 4.1 Hz, 1H), 8.05 (dd, *J* = 1.9, 7.6 Hz, 1H), 7.94 (ddd, *J* = 7.6, 4.1, 1.9 Hz, 1H), 5.33 (s, 2 H), 2.20 (s, 3H).

4.4.2. 2-Hydroxymethyl-4-nitropyridine 23[43]

2-Acetoxymethyl-4-nitropyridine **20** (1.39 g, 7.1 mmol) was stirred with methanol (20 mL) and 1 M NaOH (9 mL) under N_2 for 90 min. The mixture first became dark green and rapidly turned to orange. Water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an orange oil which, after flash chromatography (SiO_2, hexane/ether = 4:1), afforded **23** as a pale yellow solid (0.86 g, 79%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.85 (d, *J* = 5.4 Hz, 1H), 8.05 (d, *J* = 2.1 Hz, 1H), 7.92 (dd, *J* = 2.1, 5.4 Hz, 1H), 4.91 (d, *J* = 5.4 Hz, 2H), 3.19 (t, *J* = 5.4 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.2, 163.3, 151.0, 114.9, 113.2, 64.4.

4.5. General procedure for the synthesis of ligands using method A

Dimesylate (1 equiv) and the corresponding amine (5 equiv) were added together at 0 °C under N_2 atmosphere. The mixture was then allowed to warm slowly to rt and react for 96 h, after which time the mixture was transferred to ice-cold 2 M NaOH and the resulting solution was extracted with hexane (four times). The combined hexane layers were dried (KOH pellets or $MgSO_4$). After filtration, the solvent was removed in vacuo and the resulting oil was purified by flash chromatography (SiO_2, hexanes/ether) to afford the desired compound.

4.6. General procedure for the synthesis of ligands using method B

A *trans*-2,5-disubstituted pyrrolidine (1 equiv), K_2CO_3 (2 equiv), and a bromide (1 equiv) were allowed to react in MeCN under N_2 at 40 °C for 24 h. The solid was removed by filtration and the filtrate was concentrated in vacuo. The resulting oil was taken up in ether, washed with satd aq $NaHCO_3$ solution (twice) and brine (once), and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo and the resulting oil was purified by flash chromatography (SiO_2, hexanes/ether) to afford the desired product.

4.7. Synthesis of pyrrolidine–pyridine ligands

4.7.1. (+)-2-[(2*R*,5*R*)-2,5-Diphenylpyrrolidin-1-yl]methylpyridine 34[16]

(Method A) (−)-(1*S*,4*S*)-1,4-Bis(methanesulfonyloxy)-1,4-diphenylbutane[33] (1.51 g, 6.2 mmol) was prepared by the literature procedure. It was cooled to 0 °C and allowed to react with 2-aminomethylpyridine (3.50 g, 32.4 mmol) to afford ligand **34**, after flash chromatography (SiO_2, hexane/ether = 1:1), as a pale yellow solid (0.87 g, 44%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (ddd, *J* = 0.9, 1.8, 4.9 Hz, 1H), 7.59 (dt, *J* = 1.8, 7.7 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.32–7.20 (m, 10H), 7.07 (m, 1H), 4.37 (br t, *J* = 4.4 Hz, 2H), 3.66 (d, *J* = 15.7 Hz, 1H), 3.39 (d, *J* = 15.7 Hz, 1H), 2.60 (m, 2H), 2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 148.6, 143.3, 136.0, 128.2, 128.0, 127.0, 122.4, 121.2, 65.7, 53.3, 33.3; $[\alpha]_D^{25} = +131.6$ (*c* 0.08, $CHCl_3$); exact mass (EI) *m/z* calcd for $C_{23}H_{25}N_2$ (MH^+) 315.1861, found 315.1869; de >98% (^{1}H NMR),

ee >99% [Chiralcel OD, hexanes/isopropanol/triethylamine = 99:1:0.1, 0.5 mL/min, 19.2 min (*R*,*R*), 19.8 min (*meso*), 20.3 min (*S*,*S*)].

4.7.2. (+)-2-[(2*R*,5*R*)-2,5-Diphenylpyrrolidin-1-yl]ethylpyridine 35

(Method A) 2-(2-Aminoethyl)pyridine (0.50 g, 4.1 mmol) was allowed to react with (−)-(1*S*,4*S*)-1,4-bis(methanesulfonyloxy)-1,4-diphenylbutane (0.50 g, 1.3 mmol) in the presence of triethylamine (1.0 mL, 7.1 mmol). After aqueous workup as described before the crude product was purified by flash chromatography (SiO_2, hexane/ether = 2:1) to afford **35** as a colorless oil (0.22 g, 53%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (ddd, J = 0.5, 1.5, 5.0 Hz, 1H), 7.44 (dt, J = 2.0, 7.5 Hz, 1H), 7.31–7.20 (m, 10H), 7.02 (ddd, J = 1.0, 4.5, 7.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 4.41 (m, 2H), 2.77–2.64 (m, 4H), 2.50 (m, 2H), 1.84 (m, 2H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 160.9, 148.9, 144.7, 135.7, 128.2, 127.7, 126.7, 123.0, 120.8, 66.2, 47.4, 37.5, 33.5; $[\alpha]_D^{25} = +116.2$ (c 0.9, CH_2Cl_2); MS (FAB$^+$) m/z (rel intensity) 329.3 (MH$^+$, 100), 236.2 (13), 185.2 (42), 93.2 (38); exact mass (FAB$^+$) m/z calcd for $C_{23}H_{25}N_2$ (MH$^+$) 329.2018, found 329.2022; de >98% (^{1}H NMR).

4.7.3. (+)-2-[(2*R*,5*R*)-2,5-Diphenylpyrrolidin-1-yl]methyl-4-nitropyridine 36

(Method B) 2-Hydroxymethyl-4-nitropyridine **23** (0.46 g, 3.0 mmol) was dissolved in dry CH_2Cl_2 (50 mL) and cooled to −20 °C. Next, PBr_3 (1.03 g, 3.77 mmol) was added and the mixture was brought to reflux at 40 °C for 1 h. After the mixture was allowed to cool to rt, it was neutralized with 30% aqueous ammonia, and extracted with CH_2Cl_2 (2 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo to afford a yellow oil. Flash chromatography (SiO_2, hexane/ether = 1:1) of this oil afforded **24** as a pale yellow oil (0.49 g, 76%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.85 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 7.92 (dd, J = 1.8, 5.5 Hz, 1H), 4.63 (s, 2H). 2-Bromomethyl-4-nitropyridine **24** thus obtained was allowed to react with **12** (0.50 g, 2.2 mmol) and K_2CO_3 (0.50 g, 3.6 mmol) in MeCN (20 mL) which, after workup and flash chromatography (SiO_2, CH_2Cl_2), afforded **36** as a thick yellow oil (0.66 g, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J = 5.5 Hz, 1H), 8.00 (d, J = 2.5 Hz, 1H), 7.70 (dd, J = 2.5, 5.5 Hz, 1H), 7.25 (m, 10H), 4.37 (m, 2H), 3.70 (d, J = 16.5 Hz, 1H), 3.63 (d, J = 16.5 Hz, 1H), 2.60 (m, 2H), 2.09 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 164.6, 150.7, 143.0, 128.4, 127.9, 127.3, 126.3, 115.0, 113.7, 66.5, 53.8, 33.5; $[\alpha]_D^{23} = +61.5$ (c 1.3, CH_2Cl_2); MS (FAB$^+$) m/z (rel intensity) 360.3 (MH$^+$, 6), 246.2 (9). 185.1 (100), 93.2 (77); exact mass (FAB$^+$) m/z calcd for $C_{22}H_{22}N_3O_2$ (MH$^+$) 360.1712, found 360.1703; de >98% (^{1}H NMR), ee >98% (since there is no sign of degradation of stereochemistry indicated by the high de, the ee was determined to be higher than 98% depending on the optical purity of **12** which was measured by the literature method[33]).

4.7.4. (+)-2-[(2*R*,5*R*)-2,5-Diphenylpyrrolidin-1-yl]methyl-4-methoxypyridine 37

(Method B) 2-Hydroxymethyl-4-methoxypyridine (0.36 g, 2.6 mmol) was allowed to react with PBr_3 (0.40 mL, 4.2 mmol) in refluxing CH_2Cl_2 (5 mL) for 2 h and cooled to rt. After neutralization with 30% aqueous ammonia, the product was extracted into CH_2Cl_2 (2 × 30 mL), dried ($MgSO_4$), and filtered to yield a clear solution. Both TLC analysis (SiO_2, hexanes/ether = 1:1) and ^{1}H NMR showed no indication of the remaining starting material. Acetonitrile (30 mL) was added and the solvent was partly removed in vacuo until the total volume was about 30 mL (most CH_2Cl_2 was removed). **12** (0.32 g, 1.4 mmol) and K_2CO_3 (0.60 g, 4.3 mmol) were added to the solution and the mixture was stirred at 40 °C for 24 h. After normal aqueous workup, flash chromatography (SiO_2, CH_2Cl_2/EtOAc = 5:1) of the crude product afforded **37** as an orange oil (0.35 g, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 5.5 Hz, 1H), 7.30–6.95 (m, 10H), 6.94 (d, J = 2.5 Hz, 1H), 6.58 (dd, J = 3.0, 6.0 Hz, 1H), 4.37 (br dd, J = 4.0, 5.5 Hz, 2H), 3.82 (s, 3H), 3.59 (d, J = 15.5 Hz, 1H), 3.36 (d, J = 15.5 Hz, 1H), 2.58 (m, 2H), 2.04 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 162.2, 150.0, 143.3, 128.2, 128.0, 127.0, 125.4, 108.0, 107.4, 65.7, 54.9, 53.2, 33.2; $[\alpha]_D^{23} = +81.7$ (c 1.0, CH_2Cl_2); MS (FAB$^+$) m/z (rel intensity) 345.3 (MH$^+$, 55), 246.1 (9). 185.1 (100), 93.2 (80); exact mass (FAB$^+$) m/z calcd for $C_{23}H_{25}N_2O$ (MH$^+$) 345.1967, found 345.197; de >98% (^{1}H NMR), ee >98% (^{1}H NMR).

4.7.5. (+)-2-[(2*R*,5*R*)-2,5-Diphenylpyrrolidin-1-ylmethyl]-6-methylpyridine 38

(Method A) (1*S*,4*S*)-1,4-diphenyl-1,4-butandiol (0.50 g, 2.1 mmol) was transformed to (−)-(1*S*,4*S*)-1,4-bis(methanesulfonyloxy)-1,4-diphenylbutane[33] by the literature procedure. It was cooled to 0 °C and allowed to react with 2-aminomethyl-6-methylpyridine (**48**, 1.81 g, 14.8 mmol) for 2 h and then at rt for 6 d, followed by flash chromatography (SiO_2, hexane/ether = 1:1) to give a pale yellow oil, which solidified quickly in a freezer (0.49 g, 76.9%,%de = 75.5). Recrystallization of this product from hexane afforded **38** as colorless crystals. (0.100 g, 15.8%). Compound **38** obtained in this way was identical with a sample obtained by method B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.4, 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.23 (m, 10H), 6.87 (d, J = 7.4 Hz, 1H), 4.35 (t, J = 4.2 Hz, 2H), 3.60 (d, J = 16.2 Hz, 1H), 3.38 (d, J = 16.2 Hz, 1H), 2.55 (m, 2H), 2.37 (s, 3H), 1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 157.9, 144.4, 137.1, 129.1, 128.8, 127.8, 121.5, 119.9, 66.6, 54.2, 34.2, 27.8; mp = 57–58 °C; $[\alpha]_D^{23} = +132$ (c 1.15, $CHCl_3$); MS (FAB$^+$) m/z (rel intensity) 329 (MH$^+$, 63), 185 (100), 137 (28), 93 (84); exact mass (FAB$^+$) m/z calcd for $C_{23}H_{25}N_2$ (MH$^+$) 329.2018, found 329.2018; de >98 (^{1}H NMR), ee >98% (by comparing the rotation value with a sample obtained by method B). Anal. Calcd for $C_{23}H_{24}N_2$ (328.2): C, 84.11; H, 7.37; N, 8.53. Found: C, 83.53; H, 7.06, N, 8.38.

4.7.6. (+)-2-[(2*R*,5*R*)-2,5-Diphenylpyrrolidin-1-ylmethyl]-6-methylpyridine 38

(Method B) 2-Hydroxymethyl-6-methylpyridine (0.55 g, 4.5 mmol) was allowed to react with PBr_3 (1.21 g, 4.5 mmol) in refluxing CH_2Cl_2 (10 mL) for 2 h. After TLC (SiO_2, hexanes/ether = 1:1) showed no indication of the remaining starting material, the mixture was cooled to rt and neutralized with 30% aqueous ammonia. The product was extracted into CH_2Cl_2 (2 × 40 mL), washed with brine (2 × 25 mL), dried ($MgSO_4$), and filtered to afford a clear solution. Acetonitrile (40 mL) was added and the solvent was partly removed in vacuo until the total volume was about 40 mL (most CH_2Cl_2 was removed). **12** (0.50 g, 2.2 mmol) and K_2CO_3 (0.62 g, 4.4 mmol) were added to the solution and the mixture was stirred at 40 °C for 24 h. After aqueous workup the crude product was purified by flash column chromatography (SiO_2, hexane/ether = 1:1) to afford **38** as a pale yellow solid (0.59 g, 80%). mp = 57–58 °C; $[\alpha]_D^{23} = +132$ (c 1.15, $CHCl_3$); de >98% (^{1}H NMR), ee >98% (since there is no sign of degradation of stereochemistry indicated by the high de, the ee was determined to be higher than 98% depending on the optical purity of **12** which was measured by the literature method[33]).

4.7.7. (+)-2-[(2*R*,5*R*)-2,5-Diphenylpyrrolidin-1-ylmethyl]-4-methoxy-6-methylpyridine 39

(Method B) 2-Hydroxymethyl-4-methoxy-6-methylpyridine (0.40 g, 2.6 mmol) was allowed to react with PBr_3 (0.49 mL, 2.6 mmol) in refluxing CH_2Cl_2 (10 mL) for 1 h. After TLC (SiO_2, hexane/ether = 1:1) showed no indication of remaining starting material, the mixture was cooled to rt and neutralized with 30% aqueous ammonia. The product was extracted into CH_2Cl_2 (2 × 30 mL), washed with brine (2 × 15 mL), dried ($MgSO_4$), and

filtered to yield a clear solution. Acetonitrile (30 mL) was added and the solvent was partly removed in vacuo until the total volume was about 30 mL (most CH_2Cl_2 was removed). **12** (0.46 g, 2.1 mmol) and K_2CO_3 (0.62 g, 4.4 mmol) were added to the solution and the mixture was stirred at 40 °C for 24 h. After normal aqueous workup, flash chromatography (SiO_2, hexanes/ether = 1:1) of the crude product afforded recovered **12** (0.16 g) as a pale yellow solid and **39** as a pale yellow oil (0.43 g, 92% based on consumed **12**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.22 (m, 10H), 6.90 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 4.36 (m, 2H), 3.82 (s, 3H), 3.57 (d, J = 16.1 Hz, 1H), 3.37 (d, J = 16.1 Hz, 1H), 2.55 (m, 2H), 2.34 (s, 3H), 2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 161.7, 158.6, 143.5, 128.2, 127.9, 126.9, 106.4, 105.3, 65.8, 54.9, 53.2, 33.2, 24.5; $[\alpha]_D^{23} = +94.7$ (c 1.28, CH_2Cl_2); MS (FAB$^+$) m/z (rel intensity) 359 (MH$^+$, 48), 185 (100), 137 (30), 93 (73); exact mass (FAB$^+$) m/z calcd for $C_{24}H_{27}N_2O$ (MH$^+$) 359.2123, found 359.2118; de >98 (^{1}H NMR), ee >98% (since there is no sign of degradation of stereochemistry indicated by the high de, the ee was determined to be higher than 98% depending on the enantiomeric purity of **12** which was measured by a literature method[33]). Anal. Calcd for $C_{24}H_{26}N_2O$ (358.5): C, 80.41; H, 7.31; N, 7.81. Found: C, 80.21; H, 7.28; N, 7.78.

4.7.8. (+)-2-[(2*R*,5*R*)-(2,5-Diphenylpyrrolidin-1-ylmethyl)]quinoline 40

(Method B) 2-Quinolinecarboxylic acid (**29**, 1.04 g, 6.0 mmol) and thionyl chloride (10 mL, 137 mmol) in a round-bottomed flask was allowed to reflux under N_2 for 2 h. After the mixture was cooled to rt, excess thionyl chloride was removed in vacuo to afford an orange solid. This solid was cooled to 0 °C, and dry methanol (15 mL, excess) was added dropwise with stirring. The resulting solution was heated and allowed to reflux for 3 h, after which time the solvent was removed in vacuo to afford a yellow solid. After the flask containing the solid was cooled to 0 °C, 95% ethanol (20 mL) was added and $NaBH_4$ (0.91 g, 24 mmol) was added in portions. The mixture was stirred under N_2 overnight until TLC (SiO_2, hexane/ether = 1:1) showed no indication of the starting material. The solid was then filtered and solvent in the filtrate was removed in vacuo to afford a yellow oil. Flash chromatography (SiO_2, ether) of this oil afforded 2-hydroxymethylquinoline **30** as a yellow oil (0.50 g, 51%) with ^{1}H NMR data matching that reported.[56] Commercially available HBr (48%, 10 mL) was then added to this compound with stirring at 0 °C and then the mixture was allowed to reflux under N_2 for 3 h. After the mixture was cooled to rt, it was neutralized to pH 6–8 with 30% ammonium hydroxide. The resulting aqueous solution was extracted with CH_2Cl_2 (2 × 10 mL), dried ($MgSO_4$), and concentrated to afford 2-bromomethylquinoline **31**[47] as a brown oil (80% from **30**. **12** (0.49 g, 2.2 mmol), CH_3CN (25 mL) and K_2CO_3 (0.53 g, 3.8 mmol) were added and the mixture was stirred at 40 °C under N_2 for 2 d. After normal workup, the crude product was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc = 40:1) to give recovered **12** (0.25 g) as a yellow solid and **40** as a pale yellow solid (0.56 g, 75% based on consumed **12**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (ddd, J = 0.9, 1.8, 4.9 Hz, 1H), 7.60 (ddd, J = 1.8, 7.7, 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H) 7.09 (m, 9H), 4.30 (t, J = 4.2 Hz, 2H), 3.62 (d, J = 15.7 Hz, 1H), 3.32 (d, J = 15.7 Hz, 1H), 2.55 (m, 2H), 2.31 (s, 6H), 2.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 137.6, 136.9, 129.8, 128.9, 126.8, 123.5, 122.2, 66.4, 54.0, 34.0, 21.9; $[\alpha]_D^{28} = +141.2$ (c 1.8, $CHCl_3$); MS (FAB$^+$) m/z (rel intensity) 365 (MH$^+$, 100), 246 (13), 185 (88), 93 (54), 75 (8); exact mass (FAB$^+$) m/z calcd for $C_{26}H_{25}N_2$ (MH$^+$) 365.2018, found 365.2019; de >98% (^{1}H NMR), ee >98% (since there is no sign of degradation of stereochemistry indicated by the high de, the ee was determined to be higher than 98% depending on the enantiomeric purity of **12** which was measured by a literature method[33]). Anal. Calcd for $C_{26}H_{24}N_2$ (364.48): C, 85.68; H, 6.64; N, 7.69. Found: C, 85.28; H, 6.28; N, 7.58.

4.7.9. (+)-2-[(2*R*,5*R*)-2,5-Bis(4-methylphenyl)pyrrolidin-1-ylmethyl]pyridine 41

(Method A) A solution of (1*S*,4*S*)-1,4-bis(4-methylphenyl)-1,4-butandiol **4** (0.53 g, 2.0 mmol), triethylamine (1.05 mL, 10 mmol), and freshly distilled CH_2Cl_2 (20 mL) was slowly added to a cold (−40 °C) solution of methanesulfonyl chloride (0.55 mL, 4.8 mmol) in freshly distilled CH_2Cl_2 (20 mL). The mixture was stirred at −20 °C under N_2 for 30 min then quenched with saturated NH_4Cl solution (5 mL). The mixture was allowed to warm to rt, and the solvent was removed in vacuo until the volume was about 5 mL. The solution was diluted with ethyl acetate (90 mL), and washed with 1:2:1 water/brine/satd $NaHCO_3$ (4 × 15 mL), satd $NaHCO_3$ (2 × 15 mL), and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo until the volume was about 5 mL. The solution was then cooled to 0 °C, and hexane (20 mL) was added to the solution dropwise with stirring to form a white precipitate. After the solvent was decanted, fresh hexane (5 mL) was added and the system was cooled to 0 °C and kept in the dark. 2-Aminomethylpyridine (2.5 mL, 23 mmol) was added and the resulting mixture was stirred under N_2 at 0 °C for 2 h and then at rt for 2 d in the dark. The mixture was extracted with hexane (5 × 15 mL) and the combined hexane layers were washed with satd $NaHCO_3$ (2 × 10 mL), brine (2 × 10 mL), and dried ($MgSO_4$). Removal of the solvent after filtration gave a yellow oil. Flash chromatography (SiO_2, hexane/ether = 1:1) of the oil gave a pale yellow oil which solidified in the freezer to afford a colorless solid (0.18 g, 26.4%,%de = 75.5). Recrystallization of this product from hexane afforded **41** as colorless crystals (83 mg, 12%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (ddd, J = 0.9, 1.8, 4.9 Hz, 1H), 7.60 (ddd, J = 1.8, 7.7, 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H) 7.09 (m, 9H), 4.30 (t, J = 4.2 Hz, 2H), 3.62 (d, J = 15.7 Hz, 1H), 3.32 (d, J = 15.7 Hz, 1H), 2.55 (m, 2H), 2.31 (s, 6H), 2.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 137.6, 136.9, 129.8, 128.9, 126.8, 123.5, 122.2, 66.4, 54.0, 34.0, 21.9; mp = 145–146 °C; $[\alpha]_D^{23} = +159.7$ (c 0.96, $CHCl_3$); MS (FAB$^+$) m/z (rel intensity) 343 (MH$^+$, 75), 185 (100), 137 (28), 93 (90); exact mass (FAB$^+$) m/z calcd for $C_{24}H_{27}N_2$ (MH$^+$) 343.2174, found 343.2174; de >98% (^{1}H NMR), ee >99% [Chiralcel OD, hexanes/isopropanol/triethylamine = 99:1:0.1, 0.5 mL/min, 18.2 min (*S*,*S*), 18.6 min (*meso*), 19.0 min (*R*,*R*)]. Anal. Calcd for $C_{24}H_{26}N_2$ (343.2): C, 84.17; H, 7.65; N, 8.18. Found: C, 83.23; H, 7.35, N, 8.22.

4.7.10. (+)-2-[2,5-Bis-(4-*tert*-butylphenyl)pyrrolidin-1-ylmethyl]-pyridine 42

(Method B) 2-Hydroxymethylpyridine (0.16 g, 1.5 mmol) was allowed to react with PBr_3 (0.28 mL, 3.0 mmol) in refluxing CH_2Cl_2 (20 mL) for 1 h. After TLC (SiO_2, hexanes/ether = 1:1) showed no indication of remaining starting material, the mixture was cooled to rt and neutralized with 30% aqueous ammonia. The product was extracted into ether (2 × 50 mL), washed with brine (2 × 15 mL), dried ($MgSO_4$), and filtered to yield a clear solution. Acetonitrile (30 mL) was added and the solvent was partly removed in vacuo until the total volume was about 30 mL. Compound **15** (0.39 g, 1.2 mmol) and K_2CO_3 (0.62 g, 4.4 mmol) were added to the solution and the mixture was stirred at 40 °C for 24 h. After normal aqueous workup, flash chromatography (SiO_2, hexanes/ether = 2:1) of the crude product afforded **42** as an off-white solid (0.27 g, 55%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.39 (ddd, J = 1.7, 1.7, 5.8 Hz, 1 H), 7.51 (ddd, J = 1.7, 7.6, 7.6 Hz, 1 H), 7.41 (dd, J = 1.7, 7.6 Hz, 1 H), 7.34 (d, J = 8.3 Hz, 4 H), 7.16 (d, J = 8.3 Hz, 4 H), 6.98 (dd, J = 5.8, 7.6 Hz, 1 H), 4.31 (t, J = 4.8 Hz, 2 H), 3.63 (d, J = 15.8 Hz, 1 H), 3.40 (d, J = 15.8 Hz, 1 H), 2.52 (m, 2 H), 2.02 (m, 2 H), 1.28 (s, 18 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 160.6, 149.4, 148.5, 139.9, 135.8, 127.6, 124.9, 122.2, 121.0, 64.9, 53.2, 34.3, 33.0, 31.3; mp = 64–65 °C; $[\alpha]_D^{23} = +125.4$ (c 1.15, CH_2Cl_2); MS (FAB$^+$) m/z (rel intensity) 427 (MH$^+$, 40), 338 (4), 246 (12), 185 (100), 93 (58); exact mass (FAB$^+$) m/z calcd for

$C_{30}H_{39}N_2$ (MH^+) 427.3113, found 427.3110; de >98 (^{1}H NMR), ee >98% (since there is no sign of degradation of stereochemistry indicated by the high de, the ee was determined to be higher than 98% depending on the enantiomeric purity of **15**). Anal. Calcd for $C_{30}H_{38}N_2$ (426.3): C, 84.46; H, 8.98; N, 6.57. Found: C, 84.31; H, 9.00; N, 6.55.

4.8. Typical procedure for palladium-catalyzed allylic alkylations

Palladium-catalyzed allylic alkylations were run according to the method provided by Allen et al.[57,58] The percentage ee of the addition product was determined by ^{1}H NMR using $Eu(tfc)_3$ as the chiral shift agent, or by chiral HPLC using a Daicel Chiralcel OD column.

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