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Preparation of chiral bipyridine bis-*N*-oxides by oxidative dimerization of chiral pyridine *N*-oxides

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Abstract—The direct preparation of chiral 2,2′-bipyridine bis-*N*-oxides has been developed. The method involves two stages, first, the deprotonation of substituted chiral pyridine *N*-oxides and second, the oxidative dimerization of the resulting 2-lithiopyridine *N*-oxides. Optimization of the reaction conditions led to the selection of LiTMP in THF for the deprotonation and molecular iodine as the oxidant. The corresponding 2-iodopyridine *N*-oxide is invariably formed as a by-product. A series of 11 chiral pyridine *N*-oxides was prepared that bear substituents at the C(2) and C(5) positions. Oxidative dimerization of these mono-*N*-oxides proceeded in 33–77% yield. In all cases, the dimerization was highly diastereoselective for the formation of the *P*-configuration of the chiral axis.

1. Introduction

Because of their strong electron-donating properties, pyridine *N*-oxides have been widely applied as ligands in the preparation of metal complexes.[1] In addition, pyridine *N*-oxides serve as useful oxygen atom transfer agents for alkyl halides.[2] However, it was not until recently that the donor behavior of pyridine *N*-oxides had been successfully harnessed for nucleophilic catalysis.[3] A number of chiral pyridine *N*-oxides have been prepared and employed as Lewis-base catalysts for a range of reactions involving silicon reagents such as: (1) the allylation of aldehydes,[4] (2) the enantioselective ring opening of *meso*-epoxides,[5] (3) the cyanosilylation of ketones,[6] and (4) the cyanosilylation of imine derivatives.[7] In addition to their application as Lewis-base catalysts, these novel agents have also emerged as a new class of ligands for Lewis acidic catalysts. Chiral Lewis acids containing pyridine *N*-oxides have been used for the addition of thiols[8] or β-ketoesters[9] to α,β-unsaturated carbonyl compounds. Due to the growing interest in this class of chiral agents, general synthetic methods to access these highly functionalized heterocycles are needed.

2. Background

A survey of the current literature reveals that three classes of chiral pyridine *N*-oxides have been developed. Bis-*N*-oxides of type **A** that contain a chiral axis have been prepared in racemic form and resolved (Chart 1).

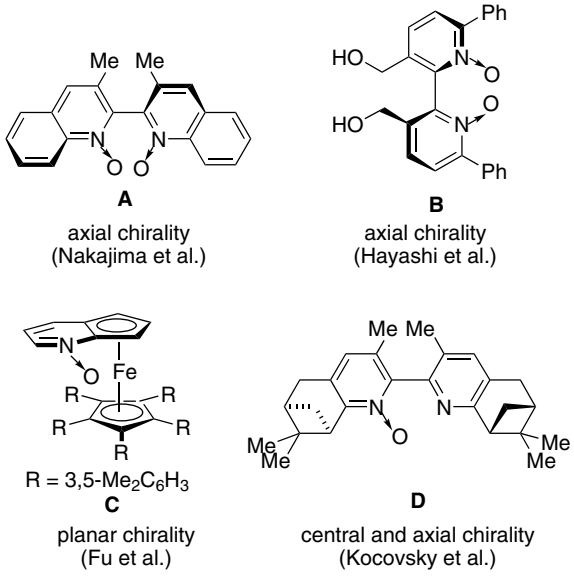

Chart 1.

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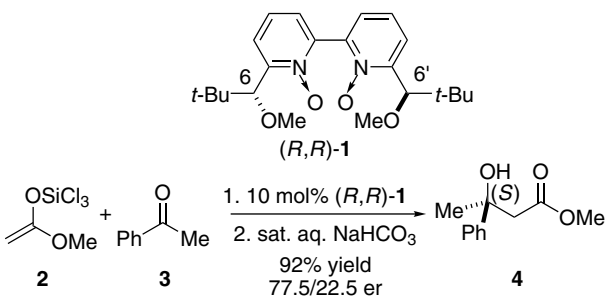
Nakajima et al. first described the resolution of this compound by recrystallization of its hydrogen bonding complex with enantiomerically pure BINOL.[4d] A conceptually distinct approach has been reported recently by Hayashi et al. who developed a method for the preparation of a new class of 2,2′-bipyrine bis-*N*-oxides **B** (Chart 1). Herein, the 3,3′-hydroxymethyl groups provide a handle for chemical resolution.[4e] These axially chiral *N*-oxides provide excellent enantioselectivity in the addition of allyltrichlorosilane to aromatic aldehydes at low catalyst loadings. Planar chiral pyridine *N*-oxide **C** has been pioneered by Fu et al. for the desymmetrization reactions of *meso*-epoxides (Chart 1).[5a] The enantiomers of this type of *N*-oxide were resolved via chiral stationary phase HPLC and have proven to be highly selective catalysts. Finally, bipyridyl mono-*N*-oxide **D** (Chart 1), which embodies both central and axial chirality, has been introduced by Kocovsky et al.[4c] By matching asymmetric induction from two chiral elements, this catalyst proved to be highly selective for the addition of allyltrichlorosilanes to aromatic aldehydes.

As part of our program to develop catalytic, enantioselective aldol additions of trichlorosilyl ketene acetals to ketones, chiral bipyridine bis-*N*-oxide (*R*,*R*)-**1** was shown to be a highly reactive and selective catalyst (Scheme 1).[10] This catalyst can be prepared by bis-N-oxidation of the parent chiral bipyridine as developed by Bolm et al.[11] In the presence of 10 mol % of this *N*-oxide, the aldol addition of methyl trichlorosilyl ketene acetal **2** to acetophenone **3** proceeds to completion within 150 min at 0 °C, to afford the β-hydroxy ester **4** in 92% yield with a 77.5/22.5 enantiomeric ratio.

The high reactivity and promising selectivity observed with this bis-*N*-oxide prompted further investigation of this structural type.[12] Structural modification of chiral bis-*N*-oxides was formulated to examine the catalyst structure/reactivity/selectivity relationship, including: (1) the effect of fixing the chiral axis, (2) the steric effects of substituents at the C(6,6′)-centers, and (3) the electronic effects from the ring substituent at C(3,3′). This report details our full investigation on the development of an efficient method for the synthesis of this class of bis-*N*-oxides via direct dimerization of the corresponding monomeric *N*-oxides and the application of this method in the preparation of fifteen bis-*N*-oxide catalysts (Chart 2) possessing both central and axial chirality.



Scheme 1.

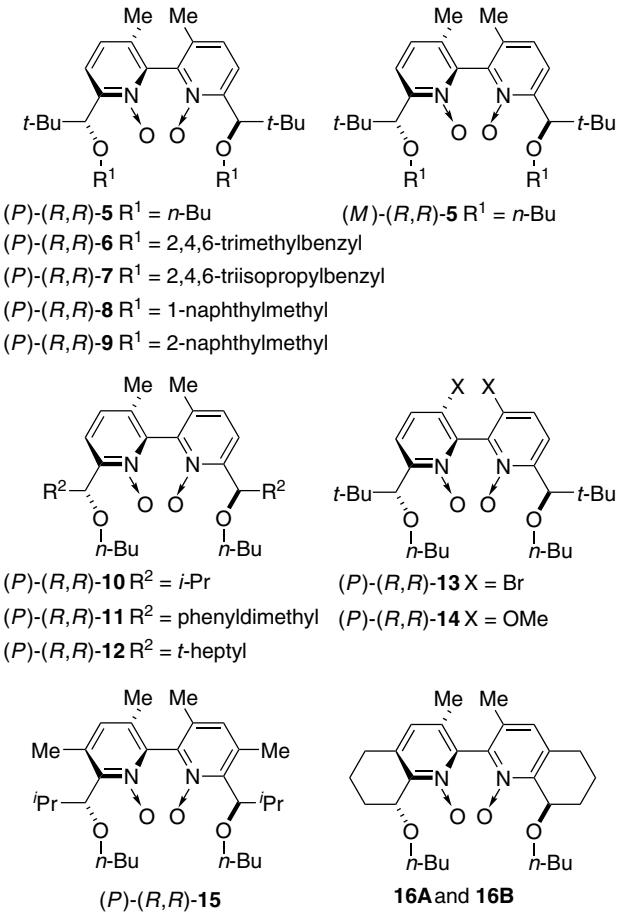


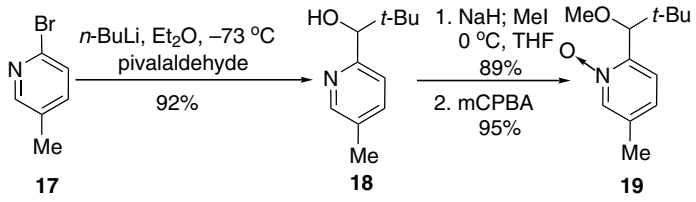
Chart 2.

3. Results

3.1. Preparation of model mono-*N*-oxide 19

Although bis-N-oxidation of bipyridines provides facile access to bis-*N*-oxides, the specific problems associated with the preparation of 3,3′-disubstituted 2,2′-bipyridyls prompted us to develop an alternative method. A more direct approach was suggested by early studies from Abramovitch et al.[13] who showed that treatment of 2-lithiopyridine-1-oxides with bromine gives predominately bipyridyl compounds. The possibility of preparing chiral bis-*N*-oxides via dimerization of chiral 2-lithiopyridine *N*-oxide was therefore investigated. To achieve this objective we first studied the conditions for quantitative deprotonation of 2-substituted pyridine *N*-oxides and then surveyed oxidants and conditions for the dimerization. Pyridine *N*-oxide **19** was chosen as a test substrate for these studies. The methyl ether was readily prepared from commercially available 2-bromo-5-methylpyridine **17**. The three-step sequence outlined in Scheme 2 afforded **19** in 81% overall yield via pyridyl alcohol **18**.

3.1.1. The effects of base on the deprotonation of pyridine *N*-oxide 19. Several lithium bases were initially surveyed in the deprotonation of **19**. A mixture of the pyridine *N*-oxide and a base was stirred at low temperature



Scheme 2.

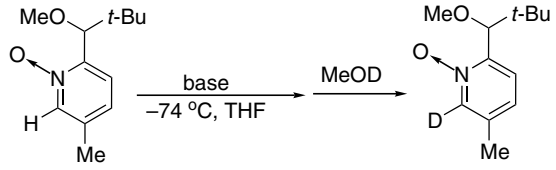
for the indicated period of time, before being quenched with MeOD. The results are summarized in Table 1. Although deprotonation of **19** took place when alkyllithiums are used, the addition of the alkyllithiums to **19** was competitive (entries 1 and 2). Lithium amide bases were also effective, but longer reaction times were necessary (entries 3–6). A clean lithiation protocol was established with the use of the bulky amide base LiTMP at low temperature over 12 h (entry 5). Attempts to increase the rate of lithiation with this reagent by increasing the temperature led to lower chemical yields of **20** (entry 6).

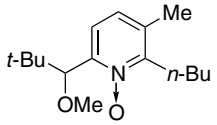
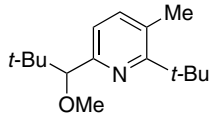
3.1.2. The effects of oxidizing agents on dimerization. With an effective lithiation protocol in hand, the choice of oxidizing agent was investigated next. The in situ generated 2-lithiopyridine *N*-oxide **21** was treated with a variety of oxidizing agents at −74 °C and the reaction mixture was then allowed to warm to room temperature before work-up. The results of the survey of oxidizing agents are summarized in Table 2. The use of molecular oxygen, $Cu(OTf)_2$ and bromine resulted in the formation of a complex mixture of unidentified products that did not contain significant amounts of the dimers (entries 1–3). When a full equivalent of iodine was employed, diastereomeric dimeric products **22** were formed in a combined yield of 43% along with 39% of the corresponding 2-iodopyridine *N*-oxide **23** (entry 4). This iodide was readily separated from the dimers by column chromatography. Interestingly, when half an equivalent of iodine was used, iodide **23** was found to be the major product (entry 5).

3.1.3. The effects of solvent on dimerization. The effects of solvent on the product ratio **22/23** were investigated to improve the higher yield of the dimers. Under a standard set of reaction conditions, weakly coordinating solvents, such as toluene and diethyl ether were compared with the strongly coordinating solvent, tetrahydrofuran in this reaction. The effect of HMPA additive was also briefly investigated. These results are summarized in Table 3.

The use of non-coordinating solvents, such as toluene and ether led to a dramatic decrease in the yield of dimers **22** (Table 3, entries 1 and 2) while iodide **23** was obtained as the major product. In the coordinating solvent THF, the dimer was produced in a slightly higher yield than the iodide (Table 3, entry 3). However, the addition of a strongly coordinating additive, such as HMPA, did not lead to an improvement in the yield of the dimer (Table 3, entry 4). Although the ratio of dimer

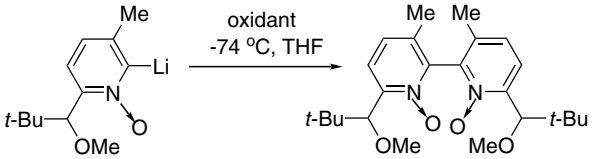
Table 1. The effects of base on deprotonation of pyridine *N*-oxide **19**



Entry	Base	Time (h)	Yield (%)[a]	By-product yield (%)[a]
1	*n*-BuLi	2	47	 23
2	*t*-BuLi	2	64	 11
3	LDA	5	77[b]	—
4	LiTMP	4.5	55[b]	—
5	LiTMP	12	95[b]	—
6[c]	LiTMP	5	64[b]	—

[a] Yield of chromatographically pure material.
[b] % D incorporation.
[c] Reaction at −40 °C.

Table 2. Effects of oxidizing agents on dimerization

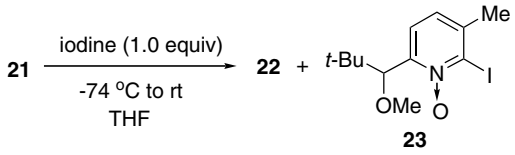


Entry	Oxidizing agent	**22** Yield (%)[a]	**23** Yield (%)
1	O_2	7	—
2	$Cu(OTf)_2$	11	—
3	Br_2	18	—
4	I_2	43	39
5[b]	I_2	23	56

[a] Combined yields of three diastereomers.
[b] 0.5 equiv of I_2 were used.

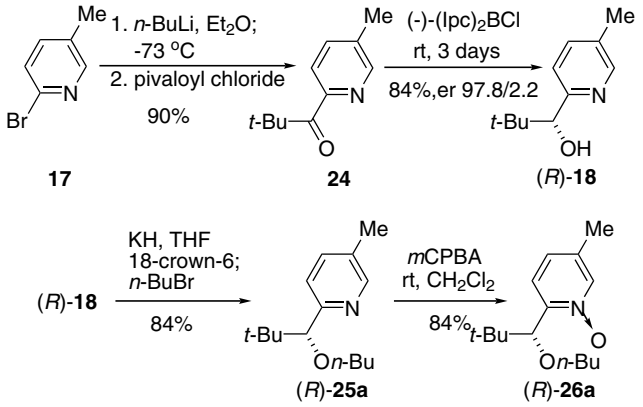
22 to iodide **23** is less than ideal, the direct dimerization of lithiopyridine-*N*-oxides still provides a viable method

Table 3. Solvent effects on the product ratio **22**/**23**



Entry	Solvent	**22** Yield (%)[a]	**23** Yield (%)[b]
1	Toluene	13	63
2	Diethyl ether	11	71
3	THF	43	39
4[c]	THF	31	45

[a] Combined yields of three diastereomers of **21**.
[b] Yields of chromatographically pure material.
[c] With 4 equiv of HMPA.



Scheme 3.

for the synthesis of bis-*N*-oxides considering that the by-product iodide can be recycled or dimerized using the Ullman protocol. Therefore, this method was chosen for the synthesis of the collection of the bis-*N*-oxides shown in Chart 2.

3.2. Synthesis of bis-*N*-oxide (*P*)-(*R*,*R*)-5 and (*M*)-(*R*,*R*)-5

All of the optimization studies above were carried out with racemic precursors **17**.[21] Consequently the products were formed as mixtures of up to four diastereomers arising from pair wise combinations of the stereogenic centers, in addition to the newly formed chiral axis. To prepare the enantiomerically pure bis-*N*-oxides shown in Chart 2 for use as chiral catalysts, access to enantiomerically enriched mono-oxides was needed. This approach was illustrated for the pair atropisomers (*P*)-(*R*,*R*)-**5** and (*M*)-(*R*,*R*)-**5**, which were initially targeted to study the effect of blocking rotation around the aryl–aryl bond. The synthesis of (*P*)-(*R*,*R*)-**5** required the preparation of an enantiomerically pure mono-oxide (*R*)-**26**. The synthetic route began with preparation of pyridyl ketone **24** by trapping 5-methyl-2-pyridyllithium with excess pivaloyl chloride (Scheme 3). Subsequent enantioselective reduction of **24** provided (*R*)-**18** in good yield and high selectivity. The formation of the butyl ether (*R*)-**25a** required the use of a sixfold excess of potassium hydride and *n*-butyl bromide. Subsequent oxidation of (*R*)-**25a** went smoothly and the monomeric chiral *N*-oxide (*R*)-**26a** was obtained in high yield.

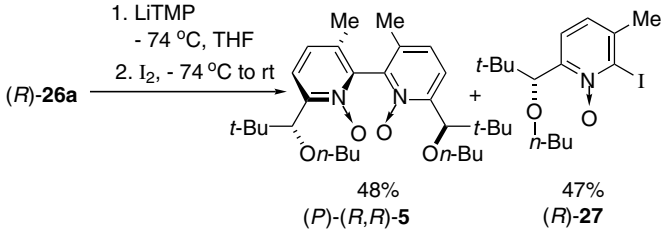
When (*R*)-**26a** was lithiated with LiTMP and treated with iodine following the procedure established for the dimerization of **19**, the bis-*N*-oxide (*P*)-(*R*,*R*)-**5** was obtained in 48% yield along with 47% yield of iodide (*R*)-**27** (Scheme 4). Interestingly, the *P*-configured atropisomer of **5** was produced with a diastereoselectivity greater than 20/1. The configuration of (*P*)-(*R*,*R*)-**5** was determined by X-ray crystallographic analysis of its complex with silicon tetrachloride.[14]

Because (*P*)-(*R*,*R*)-**5** was formed exclusively in the dimerization, it was necessary to employ a reduction/reoxidation sequence for the preparation of (*M*)-(*R*,*R*)-**5** (Scheme 5). Reduction of *N*-oxide (*P*)-(*R*,*R*)-**5** with zinc powder provided a good yield of bipyridine (*R*,*R*)-**28**. Because of the absence of the *N*-oxide moiety, the aryl–aryl bond in this compound is configurationally labile. Bis-N-oxidation of (*R*,*R*)-**28** provided a mixture of two atropisomers that were separated by silica gel column chromatography to afford (*P*)-(*R*,*R*)-**5**/(*M*)-(*R*,*R*)-**5** in 67% and 27% yields, respectively.

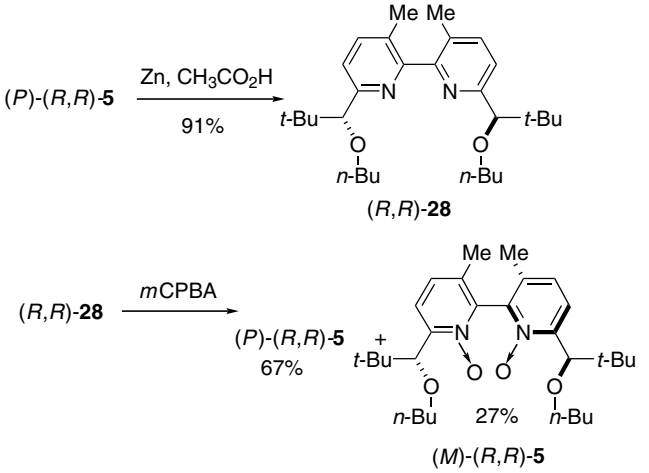
3.3. Syntheses of bis-*N*-oxides (*P*)-(*R*,*R*)-(6–16)

To prepare the remaining variations of bis-*N*-oxides compiled in Chart 1, a series of enantiomerically pure chiral mono-*N*-oxides (*R*)-**29** to (*R*)-**39** was needed for the final oxidative dimerization step. Under the assumption that the size of the ether protecting group would have a strong effect on enantioselectivity, the bis-*N*-oxides (*P*)-(*R*,*R*)-(**6**–**9**) were prepared (Fig. 1).

Because of the difficulty of formation of the neopentyl ether from alcohol (*R*)-**18**, reactive benzyl halides were chosen as alkylating agents to obtain synthetically useful yields in the etherification. The yields for each step of the sequence in the preparation of bis-*N*-oxides (*P*)-(*R*,*R*)-**6**–**9** are summarized in Table 4. These prod-



Scheme 4.



Scheme 5.

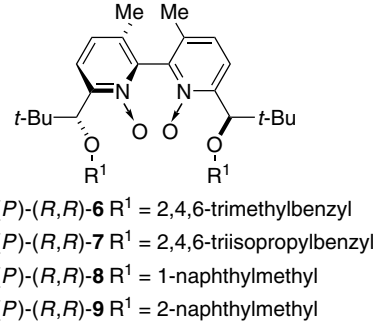


Figure 1. Structural variations of the ether protecting group.

ucts are inferred to be (*P*)-configured at the aryl–aryl bond, on the basis of the sign of their specific rotation as compared to (*P*)-(*R*,*R*)-**5**. The same sense of asymmetric induction observed in the addition of **2** to acetophenone provides additional evidence that the configurations of these catalyst are the same as that in (*P*)-(*R*,*R*)-**5**.

3.4. Synthesis of bis-*N*-oxides (*P*)-(*R*,*R*)-10–12

This group of catalysts was prepared in order to assay the effect of the size of the alkyl substituent at the 6,6′-stereocenters on enantioselectivity (Fig. 2).

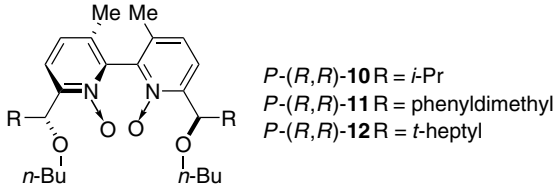


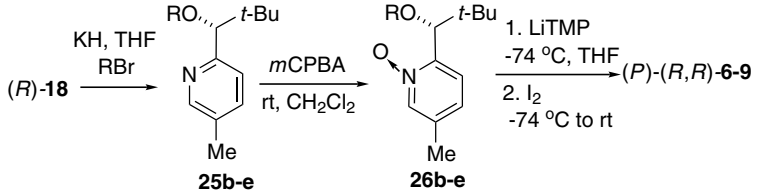
Figure 2. Structural variations of the alkyl groups at the 6,6′-stereocenters.

3.4.1. Synthesis of (*P*)-(*R*,*R*)-10. The synthesis of (*P*)-(*R*,*R*)-**10** began with the preparation of the racemic alcohol (±)-**29** from 2,5-dibromopyridine (Scheme 6). The choice of 2,5-dibromopyridine instead of 2-bromo-5-methylpyridine as a starting material was based on the desire to have the ability to vary the substituent at the 3,3′-positions of the bis-*N*-oxides. Thus, 2,5-dibromopyridine was selectively lithiated at the 2-position using the protocol developed by Wang et al.[15] and reacted with isobutyraldehyde to produce pyridyl alcohol (±)-**29** in good yield.

A two-step sequence converted racemic **29** to (*R*)-**29** via enantioselective reduction of pyridyl ketone **30**. The formation of butyl ether (*R*)-**31** proceeded in good yield. In order to have a direct comparison with bis-*N*-oxide (*P*)-(*R*,*R*)-**4**, a methyl group was introduced at the 5-position by a Kumada-type coupling reaction of (*R*)-**31** with methylmagnium bromide.[16] Finally, *N*-oxide (*R*)-**33** was obtained in excellent yield by N-oxidation of (*R*)-**32**. Subsequent dimerization provided a 38% yield of (*P*)-(*R*,*R*)-**10** along with 57% iodide (*R*)-**34**. The absolute configuration of **10** was inferred by the sign of its specific rotation, which was the same as that of (*P*)-(*R*,*R*)-**5**.

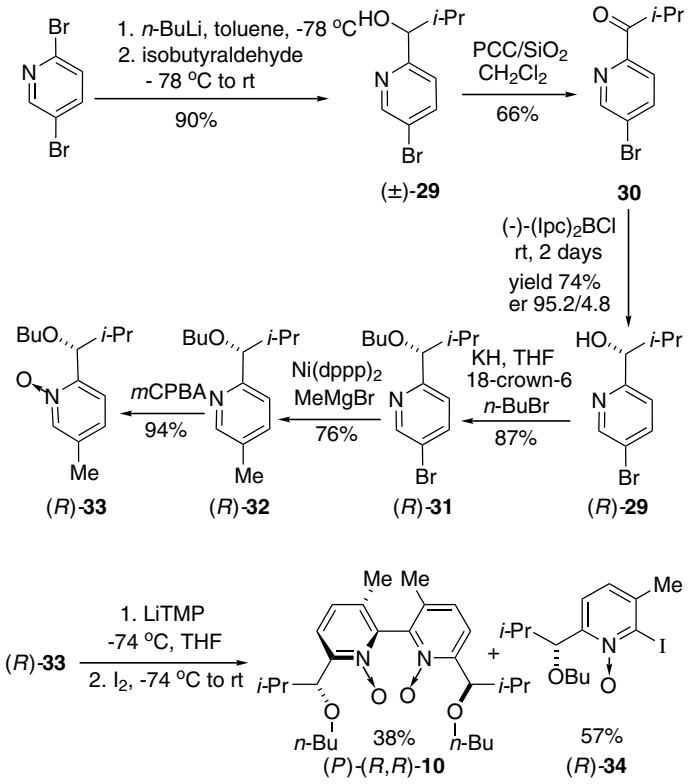
3.4.2. Synthesis of (*P*)-(*R*,*R*)-11. The synthesis of the bis-*N*-oxide (*P*)-(*R*,*R*)-**11** started with the preparation of (±)-**35** (Scheme 7). A two-step sequence converted (±)-**35** to (*R*)-**35** via enantioselective reduction of the pyridyl ketone **36**. High yields were achieved in the reduction of hindered ketone **36**. The etherification of (*R*)-**35** required the use of a large excess of the base and alkylating agent under forcing conditions to provide a good yield of the butyl ether (*R*)-**37**. Dimerization of (*R*)-**38**, which was formed from the N-oxidation of butyl ether (*R*)-**37**, delivered a 61% yield of the bis-*N*-oxide

Table 4. Yields for preparations of bis-*N*-oxides (*P*)-(*R*,*R*)-(**5**–**9**)

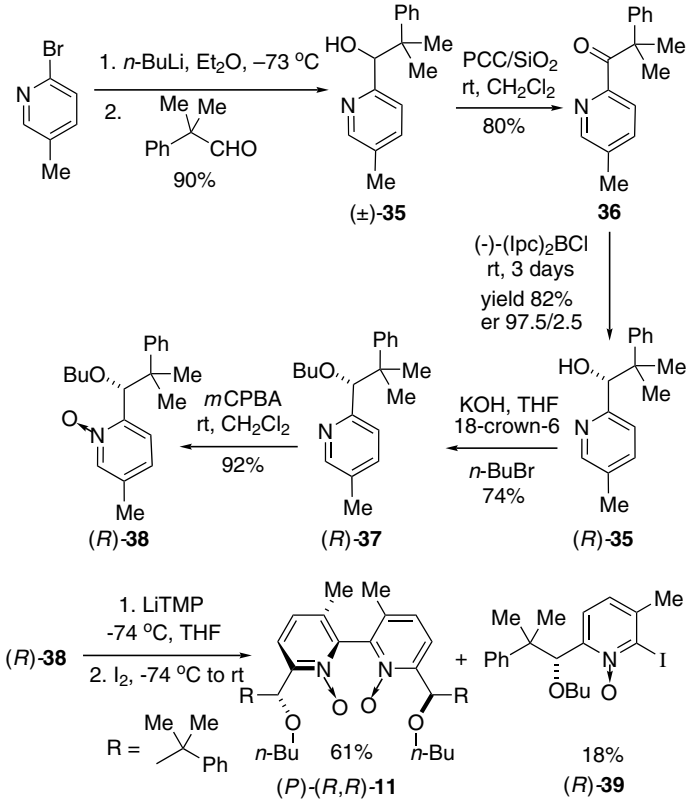


R	Product yield (%)[a]	Product yield (%)[a]	Product yield (%)[a]
2,4,6-Trimethylbenzyl	**25b**, 87	**26b**, 94	(*P*)-(*R*,*R*)-**6**, 57
2,4,6-Triisopropylbenzyl	**25c**, 82	**26c**, 86	(*P*)-(*R*,*R*)-**7**, 52
1-Naphthylmethyl	**25d**, 69	**26d**, 79	(*P*)-(*R*,*R*)-**8**, 28
2-Naphthylmethyl	**25e**, 87	**26e**, 91	(*P*)-(*R*,*R*)-**9**, 39

[a] Yields of analytically pure material.



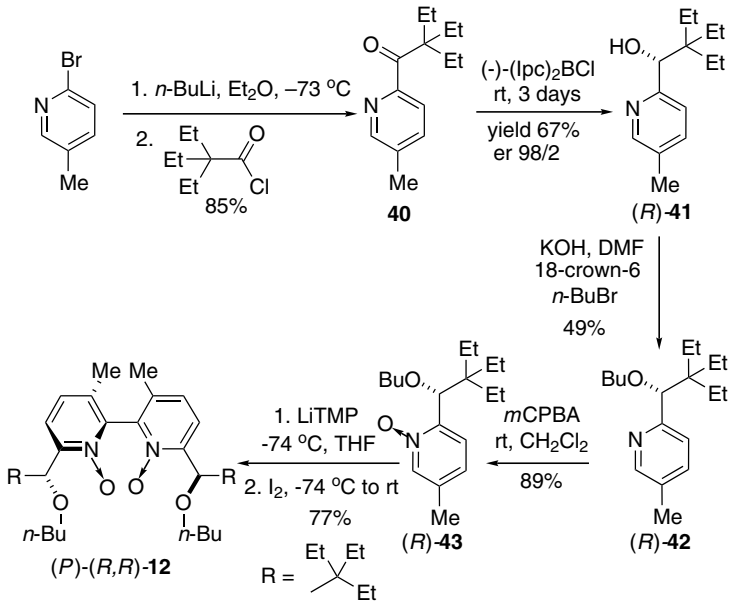
Scheme 6.



Scheme 7.

(*P*)-(*R*,*R*)-**11** along with a small amount of the iodide (*R*)-**39**.

3.4.3. Synthesis of (*P*)-(*R*,*R*)-12. The synthesis of bis-*N*-oxide (*P*)-(*R*,*R*)-**12** began with the preparation of pyr-



Scheme 8.

idyl ketone **40** (Scheme 8). Highly enantiomerically enriched (*R*)-**41** was obtained by (−)-Ipc_2BCl reduction of **40**. Etherification of (*R*)-**41** proved to be difficult and only a modest yield was obtained, even with the use of a large excess of reagents. Subsequent N-oxidation of butyl ether (*R*)-**42** went smoothly and provided (*R*)-**43** in good yield. Oxidative dimerization of (*R*)-**43** gave the dimer (*P*)-(*R*,*R*)-**12** in 77% yield. This is noteworthy since it represents the highest yield in a coupling step for any of the *N*-oxides.

3.4.4. Synthesis of (*P*)-(*R*,*R*)-13 and (*P*)-(*R*,*R*)-14. Bis-*N*-oxides (*P*)-(*R*,*R*)-**13** and (*P*)-(*R*,*R*)-**14** were investigated in order to study the electronic effect of ring substituents on the reactivity of the catalyst (Fig. 3). Although it would be ideal to compare the reactivity of bis-*N*-oxides substituted with electron-withdrawing or electron-donating groups at the 4,4′-positions, due to their well established influence on basicity, the 3,3′-positions were chosen as the site of substitution, since it was expected that both catalysts (*P*)-(*R*,*R*)-**13** and (*P*)-(*R*,*R*)-**14** could be readily obtained starting from 2,5-dibromopyridine.

3.4.5. Synthesis of (*P*)-(*R*,*R*)-13. Bis-*N*-oxide (*P*)-(*R*,*R*)-**13** was prepared in order to investigate the effect of decreasing the donor ability of *N*-oxide moiety on reactivity and selectivity. It was expected that the electron-withdrawing bromine substituents would decrease the electron density of the pyridine ring and thus diminish the electron-donating ability of the *N*-oxide donor.

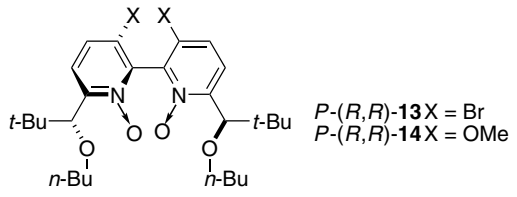
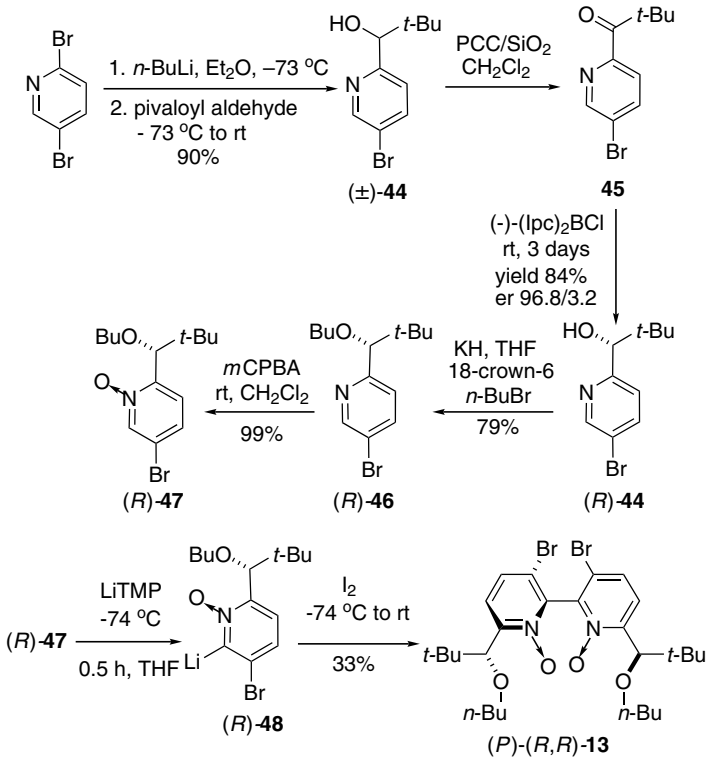


Figure 3. Structural variations at the 3,3′-positions.

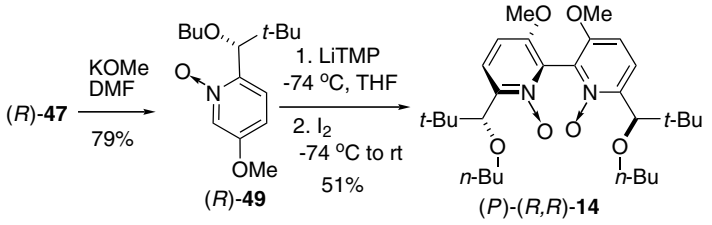
The synthesis of (*P*)-(*R*,*R*)-**13** began with the preparation of the racemic alcohol (±)-**44** by reacting pivaloyl aldehyde with 5-bromopyridyllithium, generated from selective mono-lithiation of 2,5-dibromopyridine (Scheme 9).[13] A two-step sequence of converted (±)-**44** to (*R*)-**44** via the pyridyl ketone **45** afforded the product in good yield. The formation of butyl ether (*R*)-**46** proceeded in a respectable yield under forcing conditions. Monomeric *N*-oxide (*R*)-**47** was obtained by *m*CPBA oxidation of (*R*)-**46**. It was found that the deprotonation of (*R*)-**47** with LiTMP was rapid and went to completion within 0.5 h at −74 °C. This is much faster than the rate of the 5-methyl substituted counterpart (*R*)-**25**, hinting at enhanced acidity of the proton at the 6-position due to the inductive effect from the bromine substituent. Upon treatment of the lithiopyridine *N*-oxide (*R*)-**48** with iodine, a modest yield of the dimer (*P*)-(*R*,*R*)-**13** was obtained.

3.4.6. Synthesis of (*P*)-(*R*,*R*)-14. Bis-*N*-oxide (*P*)-(*R*,*R*)-**14** was prepared in order to investigate the effect of increasing the donor ability of the *N*-oxide on reactivity and selectivity. It was expected that the 3,3′-dimethoxy substituents would enhance the donor ability of the *N*-oxide motif by donating electron density to the pyridine ring.

The monomeric *N*-oxide (*R*)-**49** required for the synthesis of (*P*)-(*R*,*R*)-**14** was readily prepared by displacement of the 5-bromo substituent of (*R*)-**47** with potassium methoxide in DMF (Scheme 10). The rate of the deprotonation of (*R*)-**49** was found to be similar to that of (*R*)-**47**, hinting at the electron-withdrawing influence from the methoxy group.



Scheme 9.



Scheme 10.

3.4.7. Synthesis of (*P*)-(*R*,*R*)-15, (*P*)-(*R*,*R*)-16, and (*M*)-(*R*,*R*)-16. Bis-*N*-oxides (*P*)-(*R*,*R*)-**15** and (*P*)-(*R*,*R*)-**16** were selected as catalyst structures to study the effect of the dihedral angle H(1′)–C(6′)–C(6)–N(1) on reactivity and selectivity (Fig. 4). The 5-methyl substituent in catalyst (*P*)-(*R*,*R*)-**15** was envisioned to rotate the H(1′)–C(6′) bond away from the co-planarity with the pyridine ring due to steric repulsion between the 5-methyl substituent and the *tert*-butyl group. Complementarily, catalyst (*P*)-(*R*,*R*)-**16** would rotate the bond in the opposite direction through ring constriction.

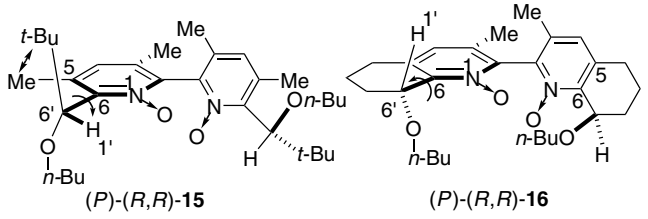


Figure 4. Variation in the dihedral angle H(1′)–C(6′)–C(6)–N(1) for (*P*)-(*R*,*R*)-**15** and (*P*)-(*R*,*R*)-**16**.

Results from molecular mechanics modeling (PM3, MM2) indicated that there was a slight increase of the dihedral angle H–C(6′)–C(6)–N in (*P*)-(*R*,*R*)-**15**·$SiCl_4$ in a clockwise direction as compared to that in (*P*)-(*R*,*R*)-**4**·$SiCl_4$. On the other hand, in (*P*)-(*R*,*R*)-**16**·$SiCl_4$ there is a drastic increase in the opposite direction (Fig. 5).

3.4.8. Synthesis of (*P*)-(*R*,*R*)-15. The synthesis of bis-*N*-oxide (*P*)-(*R*,*R*)-**15** started with the preparation of pyridyl ketone **50** through reaction of pivaloyl chloride with 3,5-dimethylpyridyllithium (Scheme 11). Subsequent enantioselective reduction of **50** with (−)-Ipc_2BCl provided alcohol (*R*)-**51**. Butyl ether (*R*)-**52** was obtained in good yield under the forcing conditions and mono-*N*-oxide (*R*)-**53** was obtained after N-oxidation of (*R*)-**52**.

Dimerization of (*R*)-**53** provided (*P*)-(*R*,*R*)-**15** in modest yield (Scheme 12). Unfortunately, iodide (*R*)-**54** was obtained as the major product under these conditions.

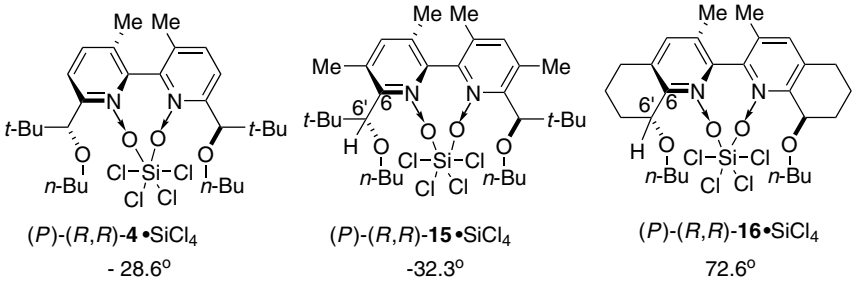
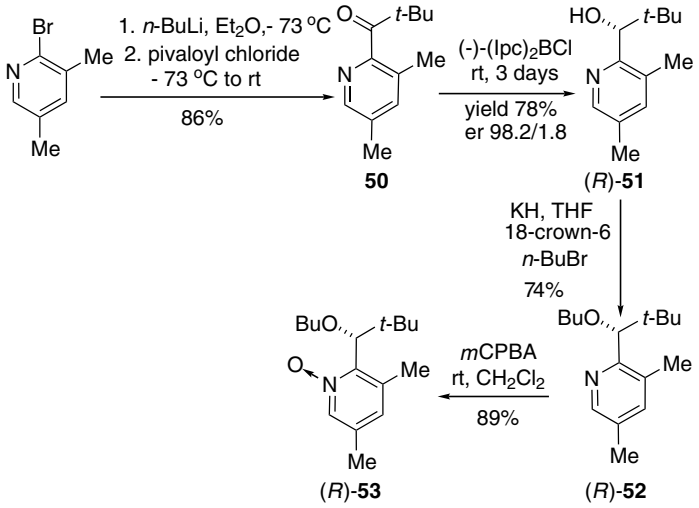
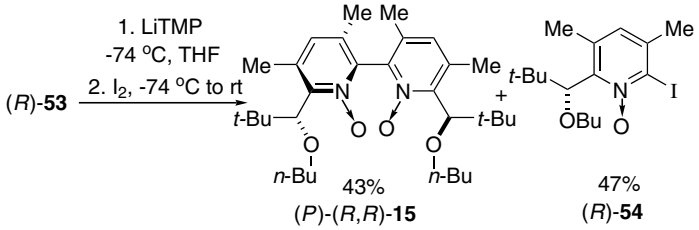


Figure 5. Dihedral angle H–C(6′)–C(6)–N in PM3-calculated structures.



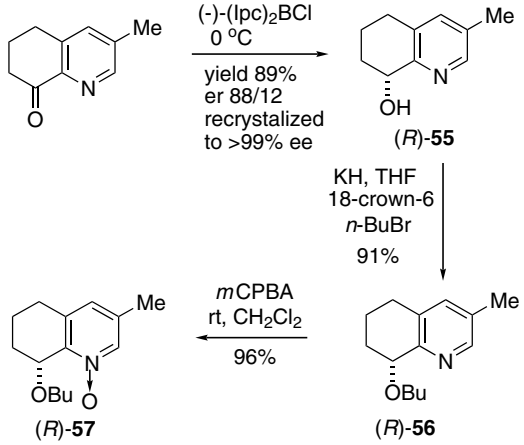
Scheme 11.



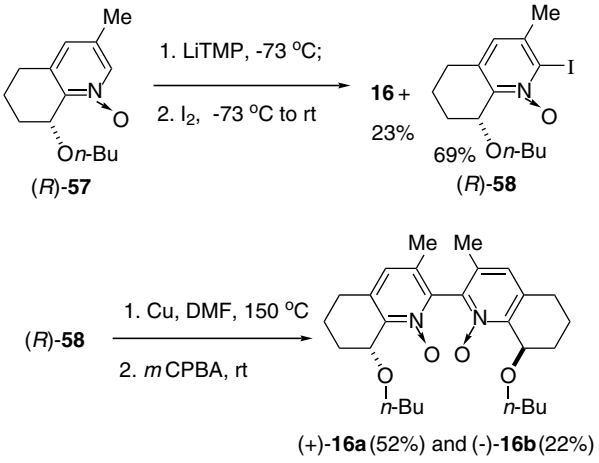
Scheme 12.

3.4.9. Bis-*N*-oxides (*P*)-(*R*,*R*)-16 and (*M*)-(*R*,*R*)-16. The synthesis of (*P*)-(*R*,*R*)-**16** began with the preparation of pyridyl alcohol (*R*)-**55** (Scheme 13). 3-Methyl-6,7-dihydro-5*H*-quinolin-8-one[17] was reduced with (−)-Ipc$_2$BCl at 0 °C to provide (*R*)-**55** in good yield but with modest enantiomeric purity. The enantiomeric purity of (*R*)-**55** could be enhanced to greater than 99/1 by two recrystallizations of (*R*)-**55** from *tert*-butyl methyl ether. Enantiomerically pure (*R*)-**55** was then transformed to the monomeric *N*-oxide (*R*)-**57** in two steps via the butyl ether (*R*)-**56**.

Surprisingly, the dimerization of (*R*)-**57** was found to proceed with low selectivity, providing a poor yield of dimeric products. Again, the major product of the reaction was found to be the iodide (*R*)-**58** (Scheme 14). Because of the poor yield of dimeric product, the iodide



Scheme 13.

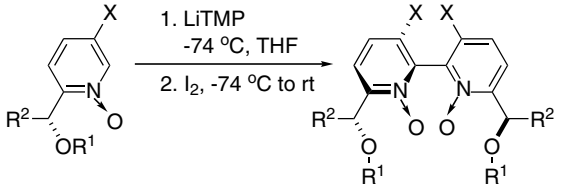


Scheme 14.

(*R*)-**58** was converted to the bis-*N*-oxide **16** by treatment with copper powder in DMF at 150 °C and then with *m*CPBA at rt. The two isomers were separated by silica gel column chromatography. The less polar isomer was found to be the major isomer. Since both isomers showed poor selectivities in the aldol reaction, their absolute configurations were not assigned.[14]

The results of the dimerizations of the enantiomerically enriched mono *N*-oxides are summarized in Table 5. The configurations of these bis-*N*-oxides were inferred to be (*P*), on the basis of the sign of their specific rotation as compared to (*P*)-(*R*,*R*)-**5**.[14] The same sense of asymmetric induction observed in the addition of **2** to acetophenone, provides additional evidence that the configurations of these catalysts are the same as those in (*P*)-(*R*,*R*)-**5**. On the other hand, the tetrahydroquinoline-derived mono-*N*-oxide (*R*)-**39** delivered a mixture of two atropisomers, in low yield (Table 5, entry 12).

Table 5. Dimerization of chiral pyridine-*N*-oxides



Entry	Mono-*N*-oxide	Bis-*N*-oxide[a]	Yield (%)[b]
1	(*R*)-**26a**	(*P*)-(*R*,*R*)-**5**	48
2	(*R*)-**26b**	(*P*)-(*R*,*R*)-**6**	57
3	(*R*)-**26c**	(*P*)-(*R*,*R*)-**7**	52
4	(*R*)-**26d**	(*P*)-(*R*,*R*)-**8**	28
5	(*R*)-**26e**	(*P*)-(*R*,*R*)-**9**	39
6	(*R*)-**33**	(*P*)-(*R*,*R*)-**10**	38
7	(*R*)-**38**	(*P*)-(*R*,*R*)-**11**	61
8	(*R*)-**43**	(*P*)-(*R*,*R*)-**12**	77
9	(*R*)-**48**	(*P*)-(*R*,*R*)-**13**	33
10	(*R*)-**49**	(*P*)-(*R*,*R*)-**14**	51
11	(*R*)-**53**	(*P*)-(*R*,*R*)-**15**	37
12	(*R*)-**58**	**16a** and **16b**	23[c]

[a] These products are inferred to be (*P*)-configured at the aryl–aryl bond based on comparison of the sign of their specific rotation as to that of (*P*)-(*R*,*R*)-**5**.
[b] Yields of chromatographically pure material.
[c] Yields of a mixture of both diastereomers.

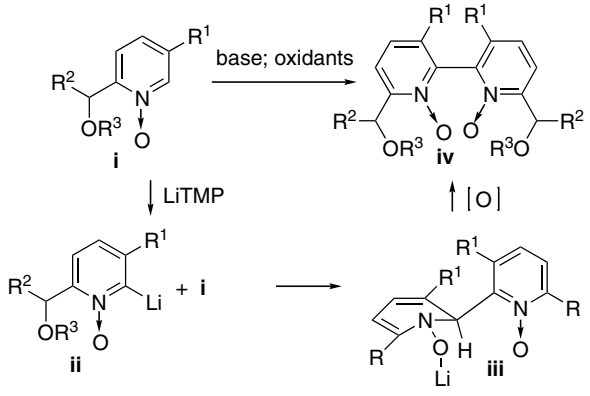
4. Discussion

Directed *ortho*-lithiation of heterocyclic *N*-oxides and subsequent reactions of lithio *N*-oxides have been extensively studied.[18] However, examples of the formation of bis-*N*-oxides by such a method are rare. Therefore, the formation of bis-*N*-oxides from the monomeric *N*-oxides of the structural type **i** represents a novel transformation, and hence raises the question of the mechanism.

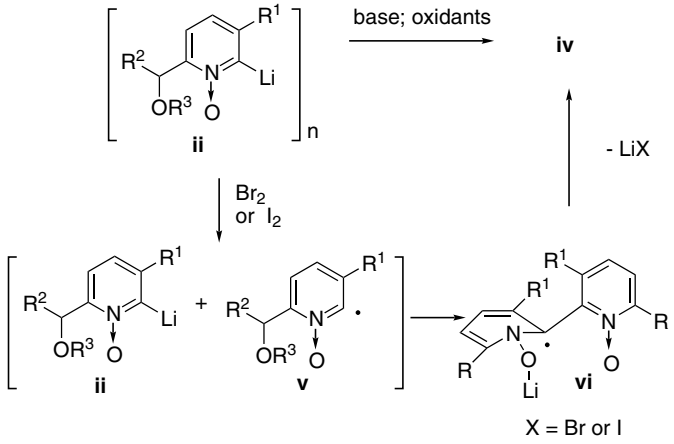
Three limiting scenarios can be formulated based on the intermediacy of the 2-lithiopyridine-*N*-oxide **ii**, formed by the deprotonation of the parent *N*-oxides: (1) addition of the 2-lithiopyridine to the neutral precursor **i** in a slow step, followed by a secondary oxidation, (2) addition of **ii** to a radical formed by single electron oxidation of **ii** and subsequent oxidation by iodine, and (3) iodination of **ii** and then addition of the 2-lithiopyridine precursor followed by loss of lithium iodide. These three mechanisms are elaborated below.

In the first scenario, 2-lithiopyridine *N*-oxide **ii** (formed by slow deprotonation of **i**) reacts with mono *N*-oxide **i** to form stable adduct **iii**. Subsequent oxidation of **iii** would provide dimer **iv** (Scheme 15). Such a mechanism has been suggested for the formation of bisquinoline *N*-oxide products.[19] Herein, this mechanism might explain the formation of a small amount of dimer when pyridine *N*-oxide **17** was treated with LiTMP.

In the second proposed mechanism, the 2-lithiopyridine *N*-oxide **ii** was oxidized by iodine or bromine to give free radical **v** (Scheme 16). As it is well known that lithio anions generally exist as aggregates,[20] it is reasonable to propose that upon oxidation of the aggregated species with a single electron oxidant, radical **v** might be generated and react with another molecule of **ii** in the immediate proximity to produce radical **vi**. It is noteworthy that the highest yields of bis-*N*-oxides were obtained from mono-*N*-oxides having most sterically encumbered oxygen substituents, such as phenyldimethyl and *tert*-heptyl groups. One might expect that these bulky



Scheme 15.



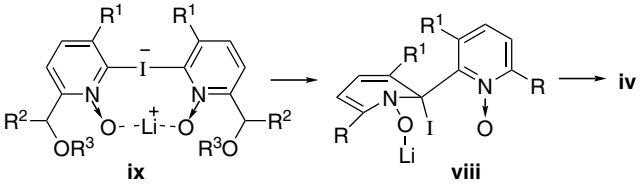
Scheme 16.

substituents would facilitate deaggregation and lead to the formation of a dimerization product.

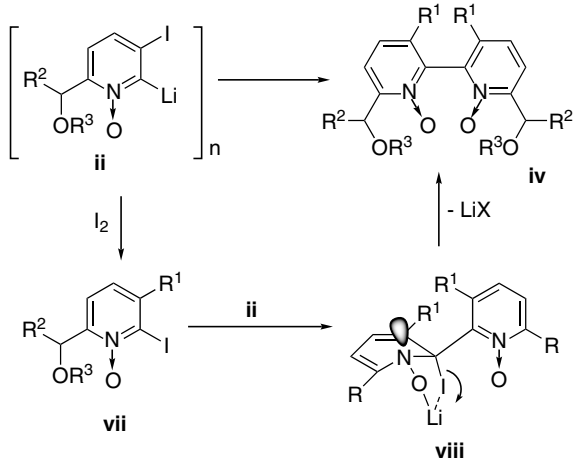
The third scenario invokes the intermediacy of an 2-iodopyridine *N*-oxide **vii**, which was always isolated as a by product (Scheme 17). Thus, the halogenation of addition of **ii** to form **vii** could be followed by an addition to **ii**, analogous to the addition to radical **v** above. In this case the intermediate **viii** would collapse with the loss of lithium iodide to form dimer **iv**.

If a hypervalent iodine intermediate[21] is taken into account, the formation of a complex of structure **ix** might precede the carbon–carbon bond formation step (Scheme 18). From studies by Reich and co-workers on lithium–iodine exchange reactions it is known that hypervalent iodine 'ate' complexes can be formed upon mixing phenyllithium and iodobenzene and in a strong coordinating solvent, such as HMPA.[22] It is conceivable that in the current case, the *N*-oxide donor might coordinate to Li^+ and thus facilitate the formation of dipyridyliodinate anion.

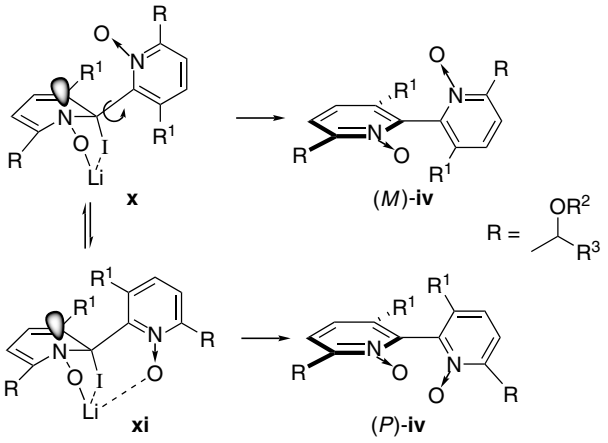
The high diastereoselectivity observed in the formation of the series of bis-*N*-oxides (*P*)-(*R*,*R*)-(**5**–**15**) is intriguing because the stereocenter at the 6-position is remote from the generated chiral axis. In principle, the two intermediates **x** and **xi** could lead to the formation of the two atropisomers of **iv** (Scheme 19). Rotation around the newly formed carbon–carbon bond interconverts the intermediates **x** and **xi**. In the absence of a clear mechanistic picture, it is difficult at best to formulate a rationale for the near exclusive formation of the *P*-isomers in the series **5**–**15**. It is also unclear if the selectivity arises from a kinetically controlled formation of intermediates, such as **x** and **xi** or from their thermodynamic equilibration. The poor selectivity in the dimerization of (*R*)-**58** suggests that the bulk and/or conformation of the substituent at C(6,6′) plays an important role in the stereochemical outcome. However, this is difficult to visualize by consideration of molecular models. On



Scheme 18.



Scheme 17.



Scheme 19.

the other hand, it is intriguing to consider the possible role that chelation of a lithiated intermediate may play in determining the preference (be it kinetic or thermodynamic) for the formation or breakdown of **xi**, which leads to the observed diastereomer (*P*)-**iv**.

5. Conclusion

A direct method for the synthesis of chiral bipyridine bis-*N*-oxides has been developed. The key step of the synthesis is an iodine-mediated dimerization reaction of in situ-generated 2-lithiopyridine *N*-oxide. The facile syntheses of these agents allow systematic structural variations, which facilitate the elucidation of the relationship between catalyst structure, reactivity, and selectivity for a variety of catalyzed reactions.

6. Experimental

6.1. General experimental

All reactions were performed in oven (140 °C) or flame-dried glassware under an inert atmosphere of dry N_2. All reaction temperatures corresponded to internal temperatures measured with Teflon-coated thermocouples unless otherwise noted. Solvents for extraction and chromatography were of technical grade and distilled from the indicated drying agents: hexane ($CaCl_2$); methylene chloride ($CaCl_2$); ethyl acetate (K_2CO_3). Reaction solvents were distilled from the indicated drying agents: methylene chloride (P_2O_5); methanol (Mg). Diipropylethylamine was freshly distilled from CaH_2. Flash column chromatography was performed using 230–400 mesh silica gel. 1,1,6,6-Tetramethylpiperidine was freshly distilled before use. 2-Bromo-5-methylpyridine was used as received. 2-Methyl-2-phenylpropionaldehyde,[1] 2,2-diethylbutyryl chloride,[2] and 3-methyl-6,7-dihydro-5*H*-quinolin-8-one[3] were prepared according to the literature procedures.

^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra were recorded on 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz; ^{19}F, 376 MHz), 500 (^{1}H, 500 MHz; ^{13}C, 126 MHz). ^{1}H NMR and ^{13}C NMR spectra are referenced to residual chloroform (δ 7.26 ppm, ^{1}H; δ 77.0 ppm, ^{13}C). ^{19}F NMR spectra are referenced externally to C_6F_6. Chemical shifts are given in parts per million (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broadened). Coupling constants, *J*, are reported in Hertz. All ^{1}H and ^{13}C NMR assignments are corroborated by 2D experiments (HETCOR and COSY).

Low-resolution electron impact (EI) mass spectra were obtained with a typical ionization voltage of 70 eV. Data are reported in the form *m*/*z* (intensity relative to base = 100). Infrared spectra (IR) are reported in cm^{-1} with the following relative intensities: s (strong, 67–100%), m (medium, 34–66%), w (weak, 0–33%). Bulb-to-bulb distillations were done on a Kugelrohr apparatus; boiling points (bp) refer to air bath temperatures (ABT) and are uncorrected. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with potassium permanganate. Analytical supercritical fluid chromatography (SFC) was performed with a built-in photometric detector ($\lambda = 220$ or 258 nm) using Daicel Chiralpak columns. Analytical capillary gas chromatography (GC) was performed with flame ionization detection (H_2 carrier gas, 16 mL/min). The following columns were used: Astec (Chiraldex) BPH 30 m × 0.25 mm × 0.125 μm. The injector temperature was 225 °C, the detector temperature was 300 °C. Retention times (t_R) and peak ratios were determined with a reporting integrator. Analytical high pressure liquid chromatography (HPLC) was performed with a built-in photometric detector ($\lambda = 220$ or 258 nm). Chiral separations were performed using a Rexchrom (*S*,*S*) β-Gem 1 column. Solvents for HPLC use were of spectroscopic grade and filtered before use. Retention times (t_R) and peak ratios were determined with a reporting integrator. All separation methods for chiral samples were calibrated with racemic samples. Melting points (mp) were determined on a capillary melting point apparatus and are corrected. Optical rotations were obtained on a digital polarimeter and are reported as follows: $[\alpha]_D^T$, concentration (*c* g/100 mL), and solvent.

6.1.1. Preparation of (*P*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-butyloxy-2,2-dimethylpropyl)-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-5. 1-[2-(5-Methylpyridyl)]-2,2-dimethylpropanone 24. To a suspension of 2-bromo-5-methylpyridine **17** (5.02 g, 29.2 mmol) in Et_2O (50 mL) was added *n*-BuLi in hexane (20.0 mL, 31 mmol, 1.05 equiv) dropwise over 15 min at −73 °C. The mixture was stirred for 1 h at −73 °C and the resulting deep red solution transferred dropwise via a short cannula to a rapidly stirred solution of pivaloyl chloride (7.2 mL, 61 mmol, 2.0 equiv) in THF (10 mL), which was pre-cooled to −73 °C. After being stirred for 4 h at −73 °C, the reddish mixture was slowly brought to rt over 5 h and the reaction quenched with cold water (20 mL). The mixture was poured into cold aq NaOH solution (40%, 100 mL) and stirred for 30 min. The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the semi-solid residue by silica gel chromatography (hexane/EtOAc, 10/1) afforded 4.72 g of product (90%) as a colorless oil. An analytically pure sample was obtained after bulb-to-bulb distillation. Data for **24**: bp: 112 °C ABT (7.3 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$): 8.43–8.44 (m, 1H, HC(5′)), 7.82 (d, $J = 8.0$, 1H, HC(2′)), 7.56–7.58 (m, 1H, HC(3′)), 2.38 (s, 3H, $H_3C(6')$), 1.45 (s, 9H, $(H_3C)_3C(2)$); ^{13}C NMR (100 MHz, $CDCl_3$): 206.6 (C(1)), 152.2 (C(2′)), 148.1 (C(6′)), 136.9 (C(4′)), 136.0 (C(5′)), 123.4 (C(3′)), 44.1 ($H_3C(C(4'))$), 27.5 (C(3)), 18.6 (C(2)); IR (neat): 2955 (m), 2928 (m), 2867 (w), 1682 (s), 1566 (w), 1481 (m), 1297 (m), 1199 (s), 964 (s) 849 (w); TLC R_f 0.44 (hexane/EtOAc, 10/1); MS (EI): 177 (14), 149 (11), 120 (10), 107 (10), 93 (100), 92 (39), 65 (18), 57 (15); Anal. Calcd for $C_{11}H_{15}NO$ (177.25): C, 74.54; H, 8.53; N, 7.90. Found: C, 74.55; H, 8.68; N, 8.04.

6.1.2. 1-[2-(5-Methylpyridyl)]-2,2-dimethylpropanol (±)-18. To a suspension of 2-bromo-5-methylpyridine (344 mg, 2.0 mmol) in Et_2O (5 mL) was added *n*-BuLi in hexane (1.4 mL, 2.2 mmol, 1.1 equiv) dropwise over 15 min at −73 °C. The mixture was stirred for 1 h at −73 °C and to the resulting deep-red solution was added pivalaldehyde (240 μL, 2.2 mmol, 1.1 equiv). The mixture was stirred for 1 h at −73 °C and then warmed to rt over 40 min. The reaction mixture was quenched with cold water and the aqueous layer extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the semi-solid residue by silica gel chromatography (hexane/EtOAc, 5/1) afforded 331 mg of product (91%) as white needles. Data for (±)-**18**: mp: 42–43 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.39 (s, 1H, HC(6′)), 7.48 (d, $J = 7.9$, 1H, HC(4′)), 7.12 (d, $J = 7.9$, 1H, HC(3′)), 4.36 (s, 1H, HC(1)), 4.31 (br s, 1H, HO), 2.35 (s, 3H, $H_3C(6')$), 0.91 (s, 9H, $(H_3C)_3C(2)$).

6.1.3. 1-[2-(5-Methylpyridyl)]-2,2-dimethylpropyl trifluoroacetate (±)-18a. To a solution of (±)-**18** (45 mg, 0.25 mmol) in 2 mL CH_2Cl_2 was added trifluoroacetic anhydride (35 μL, 0.25 mmol, 1.0 equiv) at 0 °C under nitrogen. The resulting mixture was stirred for 30 min at 0 °C and quenched by pouring the mixture into a cold, saturated $NaHCO_3$ (20 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The product (43 mg, 70%) was obtained as a colorless oil after bulb-to-bulb distillation of the residue. Data for (±)-**18a**: bp: 150 °C ABT (0.3 mmHg): ^{1}H NMR (500 MHz, $CDCl_3$): 8.40 (dd, $J = 1.5$, 0.8, 1H, HC(6′)), 7.49 (dd, $J = 7.8$, 1.4, 1H, HC(4′)), 7.17 (d, $J = 7.8$, 1H, HC(3′)), 5.67 (s, 1H, HC(1)), 2.34 (s, 3H, $H_3C(5')$), 1.01 (s, 9H, $(H_3C)_3C(2)$); GC: (*R*)-**18a**, t_R 6.10 min (50.1%); (*S*)-**18a**, t_R 7.37 min (49.8%) (Chiraldex GTA, 88 °C, 18 psi).

6.1.4. (*R*)-1-[2-(5-Methylpyridyl)]-2,2-dimethylpropanol (*R*)-18. A mixture of (−)-$(Ipc)_2BCl$ (11.8 g, 36.8 mmol, 1.5 equiv) and **24** (4.34 g, 24.5 mmol) was stirred neat at rt. The mixture became very viscous after 2 h, hence 5 mL THF was added to decrease the viscosity. After stirring for 3 days at rt, Et_2O (80 mL) was added into the flask, followed by diethanolamine (12 g). The mixture was stirred for 3 h at rt and the white precipitate filtered off through Celite. The filtrate was dried over Na_2SO_4 and concentrated under a reduced pressure. Purification of the oily residue by silica gel column chromatography (hexane/EtOAc 5/1) afforded 3.68 g of product (*R*)-**18** (84%) as a colorless oil. An analytically pure sample was obtained after bulb-to-bulb distillation. Data for (*R*)-**18**: bp: 110 °C ABT (0.5 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$): 8.37 (br s, 1H, HC(6′)), 7.43 (dd, $J = 8.0$, 1.7, 1H, HC(4′)), 7.09 (d, $J = 7.8$, 1H, HC(3′)), 4.24–4.33 (AB quartet, $J = 7.1$, 2H, HC(1) and OH), 2.33 (s, 3H, $H_3C(5')$), 0.91 (s, 9H, $(H_3C)_3C(2)$); ^{13}C NMR (100 MHz, $CDCl_3$): 156.9 (C(2′)), 147.6 (C(6′)), 136.6 (C(4′)), 131.9 (C(5′)), 122.5 (C(3′)), 79.8 (C(1)), 36.2 ($CH_3C(5')$), 25.8 (C(3)), 18.1 (C(2)); IR (KBr): 3161 (s), 2969 (s), 2948 (s), 2900 (s), 2867 (s), 2740 (m), 1606 (w), 1573 (m), 1486 (s), 1454 (s), 1423 (m), 1388 (s), 1363 (s), 1348 (m), 1307 (w), 1240 (m), 1209 (m), 1182 (w), 1132 (w), 1079 (s), 1037 (s), 1018 (s), 910 (w), 837 (m), 798 (w); TLC R_f 0.20 (hexane/EtOAc, 5/1): MS (FI, 70 eV) 181 (3), 180 (31), 179 (100), 123 (6), 122 (73); Opt. Rot. $[\alpha]_D^{24} = +28.4$ (*c* 0.89, EtOH): Anal. Calcd for $C_{11}H_{17}NO$ (177.25): C, 73.10; H, 9.56; N, 7.81. Found: C, 73.05; H, 9.73; N, 7.83.

6.1.5. (*R*)-1-[2-(5-Methylpyridyl)]-2,2-dimethylpropyl trifluoroacetate (*R*)-18a. To a solution of (*R*)-**18** (180 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic anhydride (160 μL, 1.1 mmol, 1.1 equiv) at 0 °C under N_2. The resulting solution was stirred for 1 h at 0 °C and quenched by pouring the mixture into a cold, saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The product (244 mg, 90%) was obtained as a colorless oil after bulb-to-bulb distillation. Data for (*R*)-**18a**: bp: 150 °C ABT (0.3 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$): 8.40 (dd, $J = 1.5$, 0.8, 1H, HC(6′)), 7.49 (dd, $J = 7.8$, 1.4, 1H, HC(4′)), 7.17 (d, $J = 7.8$, 1H, HC(3′)), 5.67 (s, 1H, HC(1)), 2.34 (s, 3H, $H_3C(5')$), 1.01 (s, 9H, $(H_3C)_3C(2)$); ^{13}C NMR (100 MHz, $CDCl_3$): 162.1 (q, $J = 35.9$, C(C=O)), 152.9 (C(2′)), 149.1 (C(6′)), 136.9 (C(4′)), 132.9 (C(5′)), 122.5 (C(3′)), 116.6 (q, $J = 271.8$, CF_3), 87.4 (C(1)), 35.3 ($CH_3C(5')$), 25.8 (C(3)), 18.1 (C(2)); IR (neat): 2973 (s), 2874 (m), 1786 (s), 1601 (w), 1575 (m), 1486 (m), 1467 (m), 1399 (m), 1370 (s), 1337 (w), 1222 (s), 1157 (s), 1030 (m), 949 (m), 874 (w), 834 (m), 784 (m), 772 (w), 742 (w), 719 (m); TLC: R_f 0.32 (hexane/EtOAc, 10/1); GC: (*R*)-**18a**, t_R 6.10 min (97.8%); (*S*)-**18a**, t_R 7.37 min (2.2%) (Chiraldex GTA, 88 °C, 18 psi); ^{19}F NMR (376 MHz, $CDCl_3$): −75.55; Anal. Calcd for $C_{13}H_{16}F_3NO_2$ (275.27): C, 56.72; H, 5.86; N, 5.09. Found: C, 56.90; H, 5.91; N, 5.12.

6.1.6. (*R*)-5-Methyl-1-(1-butyloxy-2,2-dimethylpropyl)-pyridine (*R*)-25a. A mixture of (*R*)-**18** (880 mg, 4.9 mmol), potassium hydroxide (540 mg, 9.8 mmol, 2.0 equiv), *n*-BuBr (790 μL, 9.3 mmol, 1.9 equiv), 18-crown-6 (130 mg, 0.49 mmol, 0.1 equiv) in DMF (10 mL) was stirred in the presence of freshly dried molecular sieve power (2 g, 3 Å) at rt. The second and third portions of *n*-BuBr (each of 790 μL, 1.9 equiv), and KOH (each of 540 mg, 2.0 equiv) were added after 4 and 8 h, respectively. After (*R*)-**18** was consumed, the reaction mixture was diluted with Et_2O (40 mL) and filtered through Celite. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column silica gel chromatography (hexane/EtOAc, 5/1) afforded (*R*)-**25a** (967 mg, 84%) as a colorless oil. An analytically pure sample was obtained after bulb-to-bulb distillation. Data for (*R*)-**25a**: bp: 110 °C ABT (0.1 mmHg); ^{1}H NMR: (400 MHz, $CDCl_3$): 8.36 (dd, $J = 1.5$, 0.7, 1H, HC(6)), 7.46 (dd, $J = 8.0$, 1.2, 1H, HC(4)), 7.26 (d, $J = 8.1$, 1H, HC(3)), 4.00 (s, 1H, HC(1′)), 3.19–3.31 (m, 2H, $H_2C(1'')$), 2.32 (s, 3H, $H_3C(C(5))$), 1.41–1.55 (m, 2H,

$H_2C(2'')$), 1.32–1.40 (m, 2H, $H_2C(3'')$), 0.90 (s, 9H, $(H_3C)_3(C(3')))$, 0.88 (t, $J = 7.3$, 3H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 158.2 (C(2)), 148.4 (C(6)), 136.3 (C(4)), 131.3 (C(5)), 121.6 (C(3)), 90.57 (C(1′)), 69.4 (C(1″)), 35.6 ($CH_3(C(5))$), 32.0 (C(2″)), 26.2 (C(3′)), 19.4 (C(3″)), 18.1 (C(2′)), 13.9 (C(4″)); IR (neat): 2957 (s), 2932 (s), 2869 (s), 1601 (w), 1569 (w),1482 (m), 1462 (w), 1390 (w), 1100 (m), 1030 (w), 858 (w), 836 (w); TLC: R_f 0.46 (hexane/EtOAc, 5/1); MS (EI): 234 (6), 179 (18), 178 (33), 122 (100), 92 (11); $[\alpha]_D^{24} = +37.8$ (*c* 0.67, EtOH); Anal. Calcd for $C_{15}H_{25}NO$ (235.37): C, 76.54; H, 10.71; N, 5.95. Found: C, 76.45; H, 10.89; N, 6.11.

6.1.7. (*R*)-5-Methyl-1-(1-butyloxy-2,2-dimethylpropyl)-pyridine *N*-oxide (*R*)-26a. General procedure 1. A solution of pyridine (*R*)-**25a** (1.67 g, 7.0 mmol) and *m*CPBA (1.84 g, 10.6 mmol, 1.5 equiv) in CH_2Cl_2 (25 mL) was prepared in a 50-mL round bottom flask fitted with a magnetic stirrer bar and the mixture stirred overnight at room temperature. Then, 10 mL of cold, 40% aqueous KOH solution was added into the flask and the resulting slurry was stirred for 1 h at room temperature. The biphasic mixture was diluted with water (50 mL) and extracted thoroughly with CH_2Cl_2 (3×25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford 1.82 g of white solid residue. Purification by silica gel column chromatography (CH_2Cl_2/MeOH, 20/1) provided the product (1.49 g, 84%) as a colorless oil. An analytically pure sample was obtained after bulb-to-bulb distillation. Data for (*R*)-**26a**: bp: 150 °C ABT (0.1 mmHg); ^1H NMR (400 MHz, $CDCl_3$): 8.06 (s, 1H, HC(6)), 7.29 (d, $J = 8.3$, 1H, HC(3)), 7.05 (d, $J = 8.0$, 1H, HC(4)), 5.02 (s, 1H, HC(1′)), 3.15–3.29 (m, 2H, $H_2C(1'')$), 2.28 (s, 3H, $H_3C(C(5))$), 1.34–1.49 (m, 2H, $H_2C(2'')$), 1.28–1.39 (m, 2H, $H_2C(3'')$), 0.96 (s, 9H, $(H_3C)_3(C(3')))$, 0.86 (t, $J = 7.3$, 3H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 149.3 (C(2)), 139.5 (C(6)), 134.4 (C(5)), 126.3 (C(3) or C(4)), 125.1 (C(3) or C(4)), 80.2 (C(1′)), 69.9 (C(1″)), 37.2 ($CH_3(C(5))$), 31.9 (C(2″)), 25.6 (C(3′)), 19.4 (C(3″)), 18.0 (C(2′)), 13.8 (C(4″)); IR (neat): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1363 (m), 1339 (m), 1285 (m), 1256 (m), 1213 (m), 1199 (m), 1177 (s), 1095 (s), 1020 (w); TLC: R_f 0.42 (CH_2Cl_2/MeOH, 20/1); MS (FAB): 253 (17), 252 (100), 236 (18), 195 (12), 178 (18), 119 (17); Opt. Rot.: $[\alpha]_D^{24} = +87.5$ (*c* 0.535, EtOH); Anal. Calcd for $C_{15}H_{25}NO_2$ (251.37): C, 71.67; H, 10.02; N, 5.57. Found: C, 71.55; H, 10.10; N, 5.76.

6.1.8. (*P*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-butyloxy-2,2-dimethylpropyl)-2,2′-bipyridine bis-*N*-oxide ((*P*)-(*R*,*R*)-5). General procedure 2. To a suspension of (*R*)-**26a** (2.51 g, 10 mmol) in Et_2O (20 mL) was added freshly prepared LiTMP solution (*n*-BuLi, 6.5 mL, 10 mmol, 1.0 equiv, and tetramethylpiperidine 1.70 mL, 10 mmol, 1.0 equiv) in THF (10 mL) at −73 °C. After being stirred for 16 h at −73 °C, a solution of iodine (1.17 g, 5.0 mmol, 0.5 equiv) in THF (10 mL) was added dropwise over 10 min into the resulting deep-red solution at −73 °C. The mixture was further stirred at −73 °C for 1 h until the color of the mixture was discharged and a second portion of iodine (1.17 g, 5.0 mmol, 0.5 equiv) in THF (10 mL) added into the flask. The cooling bath was immediately removed and the reaction mixture was brought up to rt over 40 min. During the warming period, the deep-red color reappeared. After being stirred at rt for 2 h, cold water (10 mL) was added into the flask, followed by satd aq $NaHSO_3$ solution (10 mL). The mixture was transferred to a separatory funnel, diluted with NH_4OH solution (50 mL), and was extracted thoroughly with CH_2Cl_2 (3×60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The brownish residue was purified by silica gel column chromatography (pentane/ether, 2/1) to provide 3.0 g of a mixture of (*P*)-(*R*,*R*)-**5** and the by-product iodide (*R*)-**27**. The iodide (1.70 g, 47%) was removed by recrystallization from pentane. From the mother liquor, (*P*)-(*R*,*R*)-**5** (1.20 g, 48%) was obtained. An analytically pure sample was obtained after recrystallization from hexane. Data for (*P*)-(*R*,*R*)-**5**: mp: 135–135.5 °C (hexane); ^1H NMR (400 MHz, $CDCl_3$): 7.39 (d, $J = 8.0$, 2H, HC(5)), 7.16 (d, $J = 8.1$, 2H, HC(4)), 5.06 (s, 2H, HC(1′)), 3.24–3.32 (m, 4H, $H_2C(1'')$), 2.04 (s, 6H, $H_3C(C(3)))$, 1.44–1.51 (m, 4H, $H_2C(2'')$), 1.26–1.40 (m, 4H, $H_2C(3'')$), 0.97 (s, 18H, $(H_3C)_3(C(3')))$, 0.88 (t, $J = 7.3$, 6H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 149.5 (C(6)), 142.9 (C(2)), 134.6 (C(3)), 125.9 (C(4) or C(5)), 124.8 (C(5) or C(4)), 80.3 (C(1′)), 70.0 (C(1″)), 37.2 ($CH_3(C(3))$), 32.1 (C(2″)), 25.7 (C(3′)), 19.4 (C(3″)), 17.5 (C(2′)), 14.0 (C(4″)); IR (KBr): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1285 (m), 1256 (w), 1177 (m), 1095 (m); TLC R_f 0.32 (hexane/EtOAc, 5/1); MS (FAB): 502 (34), 501 (100), 485 (22); $[\alpha]_D^{24} = -39.7$ (*c* 1.03, EtOH); Anal. Calcd for $C_{30}H_{48}N_2O_4$ (500.72): C, 71.96; H, 9.66; N, 5.59. Found: C, 72.01; H, 9.90; N, 5.64.

6.1.9. Preparation of (*P*)-(*R*,*R*)-3,3′-dimethyl-6,6′-bis(1-butyloxy-2,2-dimethylpropyl)-2,2′-bipyridine bis-*N*-oxide (*M*)-(*R*,*R*)-5 and (*R*,*R*)-3,3′-bismethyl-6,6′-bis(1-butyloxy-2,2-dimethylpropyl)-2,2′-bipyridine (*R*,*R*)-28. A mixture of (*P*)-(*R*,*R*)-**5** (1.43 g, 2.85 mmol), Zn powder (1.86 g, 28.5 mmol, 10 equiv), and CH_3CO_2H (two drops) in wet THF (20 mL) was stirred for 12 h at rt. Aqueous NH_4OH solution (50 mL) was added into the flask and stirred for 30 min. The resulting precipitate was filtered off through Celite. The filtrate was extracted thoroughly with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The brownish residue was purified by silica gel column chromatography (hexane/EtOAc, 20/1) to provide 1.22 g (91%) of the product (*R*,*R*)-**28** as a light yellow oil. Data for (*R*,*R*)-**28**: ^1H NMR (400 MHz, $CDCl_3$): 7.59 (d, $J = 7.8$, 2H, HC(5)), 7.35 (d, $J = 8.0$, 2H, HC(4)), 4.11 (s, 2H, HC(1′)), 3.18–3.38 (m, 4H, $H_2C(1'')$), 2.13 (s, 6H, $H_3C(C(3)))$, 1.47–1.54 (m, 4H, $H_2C(2'')$), 1.32–1.39 (m, 4H, $H_2C(3'')$), 0.94 (s, 18H, $(H_3C)_3(C(3')))$, 0.88 (t, $J = 7.3$, 6H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 158.1 (C(6)), 155.7 (C(2)), 138.6 (C(4)), 130.2 (C(3)), 121.3 (C(5)), 90.2 (C(1′)), 69.5 (C(1″)), 35.7 ($CH_3(C(3))$), 32.1 (C(2″)), 26.3 (C(3′)), 19.4 (C(4t3″)), 18.8 (C(2′)), 14.0 (C(4″)); IR (neat): 2957 (s), 2868 (s), 1584 (s), 1569 (s), 1479 (s),

1456 (s), 1390 (s), 1364 (s), 1303 (m), 1265 (m), 1244 (m), 1207 (m), 1101 (s), 1067 (m), 1036 (m), 994 (m), 970 (m), 841 (m), 737 (m); TLC R_f 0.37 (hexane/EtOAc, 20/1); MS (EI, 70 eV): 469 (14), 468 (39), 413 (11), 412 (40), 411 (26), 356 (27), 355 (98), 282 (21), 281 (100), 265 (11), 241 (33).

6.1.10. (*M*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-butyloxy-2,2-dimethylpropyl)-2,2′-bipyridine bis-*N*-oxide (*M*)-(*R*,*R*)-5. A solution of pyridine (*R*,*R*)-**28** (840 mg, 1.8 mmol) and *m*CPBA (864 mg, 5.0 mmol, 2.8 equiv) in CH_2Cl_2 (20 mL) was prepared in a 50-mL round bottom flask fitted with a magnetic stir bar and the mixture stirred for 12 h at room temperature. Then, 5 mL of cold, 40% aqueous KOH solution was added into the flask and the resulting slurry stirred for 1 h at room temperature. The biphasic mixture was diluted with water (25 mL) and extracted thoroughly with CH_2Cl_2 (3×25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford 1.11 g of white solid residue. Separation of the two diastereomers by silica gel column chromatography (hexane/EtOAc, 5/1) provided 601 mg (67%) of (*P*)-(*R*,*R*)-**5** and 242 mg (27%) of (*M*)-(*R*,*R*)-**5**. An analytically pure sample was obtained after recrystallization from hexane. Data for (*M*)-(*R*,*R*)-**5**: mp: 141–141.5 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 7.39 (d, $J = 8.0$, 2H, HC(5)), 7.16 (d, $J = 8.1$, 2H, HC(4)), 5.06 (s, 2H, HC(1′)), 3.24–3.32 (m, 4H, $H_2C(1'')$), 2.13 (s, 6H, $H_3C(C(3))$), 1.44–1.51 (m, 4H, $H_2C(2'')$), 1.26–1.40 (m, 4H, $H_2C(3'')$), 0.97 (s, 18H, $(H_3C)_3(C(3'))$), 0.88 (t, $J = 7.3$, 6H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 149.5 (C(6)), 142.9 (C(2)), 134.6 (C(3)), 125.9 (C(4) or C(5)), 124.8 (C(5) or C(4)), 80.3 (C(1′)), 70.0 (C(1″)), 37.2 ($CH_3(C(3))$), 32.1 (C(2″)), 25.7 (C(3′)), 19.4 (C(3″)), 17.5 (C(2′)), 14.0 (C(4″)); IR (KBr): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1285 (m), 1256 (w), 1177 (m), 1095 (m); TLC R_f 0.23 (hexane/EtOAc, 5/1): MS (FAB): 502 (33), 501 (100), 485 (25); $[\alpha]_D^{24} = +125.9$ (*c* 0.74, EtOH); Anal. Calcd for $C_{30}H_{48}N_2O_4$ (500.72): C, 71.96; H, 9.66; N, 5.59. Found: C, 72.03; H, 9.88; N, 5.66.

6.1.11. (*R*)-5-Methyl-1-(1-(2,4,6-trimethyl)benzyloxy-2,2-dimethylpropyl)pyridine *N*-oxide (*R*)-26b. Following general procedure 1, from the reaction of (*R*)-**25b** (4.26 g, 14.0 mmol) and *m*CPBA (3.19 g, 18.0 mmol, 1.3 equiv) in CH_2Cl_2 (100 mL), 3.79 g (94%) of product (*R*)-**26b** was obtained as a white solid after silica gel column chromatography (R_f 0.27, CH_2Cl_2/*i*-PrOH, 20/1). An analytically pure sample was obtained after crystallization from hexane. Data for (*R*)-**26b**: mp: 175–176 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (s, 1H, HC(6)), 7.39 (d, $J = 8.0$, 1H, HC(3)), 7.10 (d, $J = 8.0$, 1H, HC(4)), 6.84 (s, 6H, $H_3C(4'')$), 5.23 (s, 1H, HC(1′)), 4.29 (q, $J_{AB} = 15.8$, 2H, $H_2C(1'')$), 2.31 (s, 3H, $H_3C(C(3))$), 2.26 (s, 9H, $H_3C(1''')$ and $H_3C(2''')$), 0.98 (s, 9H, $H_3C(3')$); ^{13}C NMR (100 MHz, $CDCl_3$): 149.00 (C(2)), 139.66 (C(6)), 137.89, 137.65, 134.63, 131.28, 134.63, 131.28, 128.78, 126.14 (C(5)), 125.08 (C(3) or C(4)), 80.45 (C(1′)), 66.48 (C(1″)), 37.21 ($CH_3(C(5))$), 25.69 (C(1‴)), 20.93 (C(2‴)), 19.54 (C(3′)), 17.99 (C(2′)); IR (KBr): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1363 (m), 1339 (m), 1285 (m), 1256 (m), 1213 (m), 1199 (m), 1177 (s), 1095 (s), 1020 (w); TLC R_f 0.26 (Et_2O); MS (FAB): 329 (37), 328; $[\alpha]_D^{24} = +43.6$ (*c* 0.79, EtOH). Anal. Calcd for $C_{21}H_{29}NO_2$ (327.46): C, 77.02; H, 8.93; N, 4.28. Found: C, 77.11; H, 9.04; N, 4.41.

6.1.12. (*P*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-(2,4,6-trimethyl)benzyloxy-2,2-dimethylpropyl)-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-6. Following general procedure 2, from the reaction of (*R*)-**26b** (483 mg, 1.5 mmol), 277 mg (57%) of product (*P*)-(*R*,*R*)-**6** was obtained as a white solid after silica gel column chromatography (R_f 0.27, hexane/EtOAc, 3/1). An analytically pure sample was obtained after crystallization from hexane. Data for (*P*)-(*R*,*R*)-**6**: mp: 199–200 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 7.51 (d, $J = 8.3$, 2H, HC(3)), 7.22 (d, $J = 8.1$, 2H, HC(4)), 6.85 (s, 4H, HC(4″)), 5.21 (s, 2H, HC(1′)), 4.35 (q, $J_{AB} = 15.3$, 4H, $H_2C(1'')$), 2.31 (s, 12H, $H_3C(1''')$), 2.26 (s, 6H, $H_3C(C(3))$), 2.10 (s, 6H, $H_3C(2''')$), 0.98 (s, 18H, $H_3C(3')$); ^{13}C NMR (100 MHz, $CDCl_3$): 149.13 (C(6)), 143.07 (C(2)), 138.08, 137.56, 135.97, 131.45, 128.73 (C(4)), 125.72, 124.71, 126.14 (C(3)), 125.08 (C(4) or C(5)), 80.57 (C(1′)), 66.48 (C(1″)), 37.28 ($CH_3(C(5))$), 25.79 (C(1‴)), 20.97 (C(2‴)), 19.69 (C(3′)), 17.58 (C(2′)); IR (KBr) 957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1363 (m), 1339 (m), 1285 (m), 1256 (m), 1213 (m), 1199 (m), 1177 (s), 1095 (s), 1020 (w); TLC R_f 0.27 (hexane/EtOAc, 3/1); MS (FAB): 53 (18), 652 (100); $[\alpha]_D^{24} = -101.7$ (*c* 1.27, EtOH); HRMS (ESI): Calcd for $C_{42}H_{59}N_2O_4$, 653.4319. Found: 653.4316.

6.1.13. (*R*)-5-Methyl-1-(1-(2,4,6-triisopryopyl)benzyloxy-2,2-dimethylpropyl)pyridine *N*-oxide (*R*)-26c. Following general procedure 1, pyridine (*R*)-**25c** (1.15 g, 2.8 mmol) and *m*CPBA (778 mg, 4.5 mmol, 1.6 equiv) were dissolved in CH_2Cl_2 (20 mL) and the mixture was stirred overnight at rt. The product (*R*)-**26c** (987 mg, 86%) was obtained as a white solid after silica gel column chromatography (diethyl ether). An analytically pure sample was obtained after crystallization from hexane. Data for (*R*)-**26c**: mp: 105–106 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 8.42 (dd, $J = 1.5$, 1.0, 1H, HC(6)), 7.53 (dd, $J = 8.1$, 2.0, 1H, HC(4)), 7.39 (d, $J = 8.1$, 1H, HC(3)), 7.01 (s, 2H, HC(4″)), 4.32 (q, $J_{AB} = 14.9$, 2H, $H_2C(1'')$), 4.22 (s, 1H, HC(1′)), 3.18 (h, $J = 6.8$, 2H, $H_2C(6'')$), 2.88 (h, $J = 6.8$, 1H, $H_2C(8'')$), 2.37 (s, 3H, $H_3C(C(5))$), 1.25 (d, $J = 6.8$, 6H, HC(7″)), 1.18 (d, $J = 6.8$, 3H, HC(9″)), 0.92 (s, 18H, $H_3C(3')$); ^{13}C NMR (100 MHz, $CDCl_3$): 158.33 (C(2)), 149.20 (C(6)), 148.88 (C(2″) or C(5″)), 148.77 (C(2″) or C(5″)), 148.71, 148.22, 136.40 (C(3)), 131.90 (3″), 129.69 (C(4) or C(5)), 121.90, 121.50, 121.06, 92.16 (C(1′)), 64.88 (C(1″)), 57.51 ($CH_3(C(5))$), 34.34 (C(8″)), 29.21 (C(6″)), 25.81 (C(7″)), 25.33 (C(9″)), 24.16 (C(3′)), 17.15 (C(2′)); IR (KBr): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1285 (m), 1256 (w), 1177 (m), 1095 (m); TLC R_f 0.17 (Et_2O); Opt. Rot.: $[\alpha]_D^{24} = +41.1$ (*c* 2.26, EtOH); HRMS (ESI, 70 eV): Calcd for $C_{27}H_{40}NO_2$, 411.3235. Found: 412.3228.

6.1.14. (*P*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-(2,4,6-triisopropyl)benzyloxy-2,2-dimethylpropyl)-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-7. Following general procedure 2, from the reaction of (*R*)-**26c** (502 mg, 1.3 mmol), the product (*P*)-(*R*,*R*)-**7** (262 mg, 52%) was obtained as a white solid after silica gel column chromatography (R_f 0.26, pentane/Et_2O, 3/1). An analytically pure sample was obtained after recrystallization from hexane. Data for (*P*)-(*R*,*R*)-**7**: mp: 195–196 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 7.52 (d, $J = 8.2$, 2H, HC(4)), 7.25 (d, $J = 8.2$, 2H, HC(3)), 7.01 (s, 4H, HC(4″)), 5.34 (s, 2H, HC(1′)), 4.40 (q, $J_{AB} = 15.9$, 4H, $H_2C(1'')$), 3.23 (h, $J = 6.8$, 4H, $H_2C(6'')$), 2.88 (h, $J = 6.8$, 2H, $H_2C(8'')$), 2.11 (s, 6H, $H_3C(C(3))$), 1.26 (d, $J = 6.8$, 24H, HC(7″)), 1.23 (d, $J = 6.8$, 12H, HC(9″)), 0.98 (s, 18H, $H_3C(3')$); ^{13}C NMR (100 MHz, $CDCl_3$): 149.19 (C(6)), 148.62 (C(2″) or C(5″)), 148.51 (C(2″) or C(5″)), 143.32 (C(2)), 135.11 (C(3)), 128.97 (3″), 125.65 (C(4) or C(5)), 124.70 (C(5) or C(4)), 120.82 (C(4″)), 81.30 (C(1′)), 64.96 (C(1″)), 37.33 ($CH_3(C(3))$), 34.19 (C(8″)), 29.09 (C(6″)), 25.80 (C(7″)), 25.29 (C(9″)), 24.07 (C(3′)), 17.65 (C(2′)); IR (KBr): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1285 (m), 1256 (w), 1177 (m), 1095 (m); TLC R_f 0.17 (pentane/Et_2O, 5/1); MS (FAB): 822 (13), 217 (100); $[\alpha]_D^{24} = -42.3$ (*c* 0.50, MeOH). Anal. Calcd for $C_{54}H_{80}N_2O_4$ (821.22): C, 78.98; H, 9.82; N, 3.42. Found: C, 79.68; H, 10.02; N, 3.70. HRMS (ESI, 70 eV): Calcd for $C_{54}H_{80}N_2O_4$, 822.6241. Found: 822.6237.

6.1.15. (*R*)-5-Methyl-1-(1-naphthylmethoxy-2,2-dimethylpropyl)pyridine *N*-oxide (*R*)-26d. Following general procedure 1, pyridine (*R*)-**25da** (640 mg, 2.0 mmol) and *m*CPBA (530 mg, 3.0 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (20 mL) and the mixture was stirred overnight at rt. The product (*R*)-**31** (529 mg, 79%) was obtained as a white solid after silica gel column chromatography (diethyl ether). An analytically pure sample was obtained after recrystallization from hexane. Data for (*R*)-**26d**: mp: 115–116 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 8.07 (s, 1H, HC(6)), 7.97 (d, $J = 7.3$, 1H, HC(4)), 7.82 (d, $J = 7.1$, 1H, HC(3)), 6.94–7.52 (m, 7 H, naphthylH), 5.34 (s, 1H, HC(1′)), 4.83 (q, $J_{AB} = 15.9$, 2H, $H_2C(1'')$), 2.27 (s, 3H, $H_3C(C(5))$), 0.99 (s, 9H, $H_3C(3')$); ^{13}C NMR (100 MHz, $CDCl_3$): 148.53 (C(2)), 139.50 (C(6)), 135.54 (C(4)), 133.77, 133.44, 131.33, 128.4, 128.24, 126.15, 125.95, 125.79, 125.60, 125.26, 125.12, 123.87, 80.37 (C(1′)), 70.38 (C(1″)), 37.30 ($CH_3(C(5))$), 25.72 (C(3′)), 17.93 (C(2′)); IR (neat): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1363 (m), 1339 (m), 1285 (m), 1256 (m), 1213 (m), 1199 (m), 1177 (s), 1095 (s), 1020 (w); TLC R_f 0.21 (Et_2O); MS (FAB): 337 (17), 336; $[\alpha]_D^{24} = +34.7$ (*c* 0.872, EtOH); Anal. Calcd for $C_{22}H_{25}NO_2$ (335.44): C, 78.77; H, 7.51; N, 4.18. Found: C, 78.91; H, 7.56; N, 4.40.

6.1.16. (*P*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-(1-naphthylmethoxy-2,2-dimethylpropyl))-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-8. Following general procedure 2, from (*R*)-**26d** (402 mg, 1.2 mmol), 113 mg (28%) of the product (*P*)-(*R*,*R*)-**8** was obtained as a white solid after silica gel column chromatography (diethyl ether). An analytically pure sample was obtained after crystallization from hexane. Data for (*P*)-(*R*,*R*)-**8**: mp: 195–196 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 7.48 (d, $J = 8.1$, 2H, HC(5)), 7.23 (d, $J = 8.1$, 2H, HC(4)), 6.94–7.52 (m, 14H, naphthylH), 5.34 (s, 4H, HC(1′)), 4.36–4.38 (q, $J_{AB} = 14.9$, 8H, $H_2C(1'')$), 2.13 (s, 6H, $H_3C(C(3))$), 0.98 (s, 18H, $H_3C(3')$); ^{13}C NMR (100 MHz, $CDCl_3$): 149.32 (C(6)), 148.53 (C(2) or C(5)), 148.44 (C(2) or C(5)), 133.77, 133.44, 131.33, 128.4, 128.24, 126.15, 125.95, 125.79, 125.60, 125.26, 125.12, 123.87, 83.30 (C(1′)), 66.14 (C(1″)), 37.16 ($CH_3(C(3))$), 24.01 (C(3′)), 17.76 (C(2′)); IR (KBr): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1363 (m), 1339 (m), 1285 (m), 1256 (m), 1213 (m), 1199 (m), 1177 (s), 1095 (s), 1020 (w); TLC R_f 0.21 (Et_2O); MS (FAB) 670 (13), 669 (100); $[\alpha]_D^{24} = -80.9$ (*c* 1.54, EtOH); HRMS (ESI): Calcd for $C_{44}H_{49}N_2O_4$, 669.3691. Found: 669.3687.

6.1.17. (*R*)-5-Methyl-1-(1-(2-naphthylmethoxy)-2,2-dimethylpropyl)pyridine *N*-oxide (*R*)-26e. Following general procedure 1, pyridine (*R*)-**25e** (640 mg, 2.0 mmol) and *m*CPBA (530 mg, 3.0 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (20 mL) and the mixture was stirred overnight at rt. The product (*R*)-**26e** (610 mg, 91%) was obtained as a white solid after silica gel column chromatography (diethyl ether). An analytically pure sample was obtained after recrystallization from hexane. Data for (*R*)-**32**: mp: 99–100 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 8.09 (s, 1H, HC(6)), 7.80 (d, $J = 8.3$, 1H, HC(3)), 7.74 (s, HC(11″)), 7.02 (d, $J = 7.9$, 1H, HC(4)), 7.38–7.84 (m, 6H, naphthylH), 5.30 (s, 1H, HC(1′)), 4.46 (q, $J_{AB} = 16.3$, 2H, $H_2C(1'')$), 2.27 (s, 3H, $H_3C(C(5))$), 1.04 (s, 9H, $(H_3C)_3(C(3'))$); ^{13}C NMR (100 MHz, $CDCl_3$): 148.86 (C(2)), 139.84 (C(6)), 135.98 (C(5)), 134.90, 133.43, 133.16, 128.18, 127.87, 126.56, 126.34, 126.28, 126.05, 125.99, 125.40, 80.65 (C(1′)), 72.52 (C(1″)), 37.63 ($CH_3(C(5))$), 26.00 (C(3′)), 18.29 (C(2′)); IR (KBr): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1363 (m), 1339 (m), 1285 (m), 1256 (m), 1213 (m), 1199 (m), 1177 (s), 1095 (s), 1020 (w); TLC R_f 0.32 (Et_2O); MS (FAB): 337 (20), 336 (100); $[\alpha]_D^{24} = +41.3$ (*c* 0.802, EtOH); Anal. Calcd for $C_{22}H_{25}NO_2$ (335.44): C, 78.77; H, 7.51; N, 4.18. Found: C, 78.99; H, 7.68; N, 4.36.

6.1.18. (*P*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-(2-naphthylmethoxy)-2,2-dimethylpropyl)-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-9. Following general procedure 2, from (*R*)-**26e** (402 mg, 1.2 mmol), 156 mg (39%) of the product (*P*)-(*R*,*R*)-**9** was obtained as a white solid after silica gel column chromatography (diethyl ether). An analytically pure sample was obtained after crystallization from hexane. Data for (*P*)-(*R*,*R*)-**9**: mp: 195–196 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 7.44 (d, $J = 8.0$, 2H, HC(5)), 7.26 (d, $J = 8.0$, 2H, HC(4)), 7.74 (s, HC(11″)), 6.94–7.52 (m, 12H, naphthyl), 5.32 (s, 4H, HC(1′)), 4.36–4.38 (q, $J_{AB} = 16.9$, 8H, $H_2C(1'')$), 2.14 (s, 6H, $H_3C(C(3))$), 0.97 (s, 18H, $H_3C(3')$); ^{13}C NMR (100 MHz, $CDCl_3$): 148.86 (C(6)), 139.84 (C(2) or C(5)), 135.98 (C(2) or C(5)), 134.89, 133.44, 131.16, 128.18, 128.14, 127.87, 126.57, 126.34, 126.28, 126.05,

125.99, 125.40, 80.65 (C(1′)), 72.59 (C(1″)), 37.63 (CH_3(C(3))), 26.06 (C(3′)), 18.21 (C(2′)); IR (KBr): 3007 (s), 2872 (m), 1616 (w), 1505 (w), 1479 (w), 1463 (w), 1383 (m), 1363 (m), 1339 (m), 1285 (m), 1256 (m), 1213 (m), 1199 (m), 1177 (s), 1095 (s), 1020 (w); TLC R_f 0.23 (Et_2O); MS (FAB): 670 (16), 669 (100); $[\alpha]_D^{24} = -61.4$ (*c* 1.80, EtOH); HRMS (ESI): Calcd for $C_{44}H_{49}N_2O_4$, 669.3691. Found: 669.3685.

6.1.19. (*R*)-5-Methyl-1-(1-butyloxy-2-dimethylpropyl)-pyridine *N*-oxide (*R*)-33. Following general procedure 1, pyridine (*R*)-**32** (2.43 g, 8.09 mmol) and *m*CPBA (1.79 g, 10.1 mmol, 1.25 equiv) were dissolved in CH_2Cl_2 (25 mL) and the mixture was stirred overnight at rt. Work-up provided 2.52 g of white solid residue. Purification by silica gel column chromatography (CH_2Cl_2/MeOH, 20/1) provided the product (2.40 g, 94%) as a colorless oil. An analytically pure sample was obtained after bulb-to-bulb distillation. Data for (*R*)-**33**: bp 220 °C ABT (0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$): 8.34 (d, $J = 1.7$, 1H, HC(6)), 7.36 (dd, $J = 8.6$, 1.7, 1H, HC(4)), 7.28 (d, $J = 8.5$, 1H, HC(3)), 4.94 (s, 1H, HC(1′)), 3.16–3.29 (m, 2H, H_2C(1″)), 1.44–1.51 (m, 2H, H_2C(2″)), 1.29–1.36 (m, 2H, H_2C(3″)), 0.96 (s, 9H, H_3C(3′)), 0.87 (t, $J = 7.3$, 3H, H_3C(4″)); ^{13}C NMR (100 MHz, $CDCl_3$): 151.43 (C(2)), 140.89 (C(6)), 127.73 (C(4)), 125.88 (C(3)), 118.20 (C(5)), 80.23 (C(1′)), 70.12 (C(1″)), 37.33 (C(2′)), 31.84 (C(2″)), 25.56 (C(3′)), 19.33 (C(3″)), 13.83 (C(4″)); IR (neat): 3094 (w), 3036 (w), 2933 (s), 2871 (s), 1596 (m), 1532 (w), 1477 (s), 1370 (s), 1244 (s), 1094 (s), 901 (s); TLC R_f 0.18 (hexane/Et_2O, 3/1); MS (FAB): 318 (8), 316 (8), 244 (98), 242 (100); $[\alpha]_D^{24} = +27.1$ (*c* 0.637, MeOH); Anal. Calcd for $C_{14}H_{23}NO_2$ (237.34): C, 70.84; H, 9.77; N, 5.90. Found: C, 70.64; H, 9.98; N, 5.98.

6.1.20. (*P*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-butyloxy-2-methylpropyl)-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-10. Following general procedure 2, from (*R*)-**33** (474 mg, 2.0 mmol), 179 mg (38%) of the product (*P*)-(*R*,*R*)-**10** was obtained as a white solid after silica gel column chromatography (hexane/diethyl ether, 5/1). An analytically pure sample was obtained after crystallization from hexane. Data for (*P*)-(*R*,*R*)-**10**: mp: 112–113 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 7.39 (d, $J = 8.0$, 2H, HC(5)), 7.16 (d, $J = 8.1$, 2H, HC(4)), 5.06 (s, 2H, HC(1′)), 3.24–3.32 (m, 4H, H_2C(1″)), 2.16–2.25 (m, 2H, H_2C(2′)), 2.04 (s, 6H, H_3C(C(3))), 1.44–1.51 (m, 4H, H_2C(2″)), 1.26–1.40 (m, 4H, H_2C(3″)), 1.02 (d, $J = 6.8$, 3H, HC(3′)), 0.91 (t, $J = 7.3$, 6H, H_3C(4″)), 0.82 (d, $J = 6.8$, 3H, HC(3′)); ^{13}C NMR (100 MHz, $CDCl_3$): 149.50 (C(6)), 142.87 (C(2)), 134.64 (C(3)), 125.90 (C(4) or C(5)), 124.82 (C(5) or C(4)), 80.34 (C(1′)), 69.98 (C(1″)), 37.24 (CH_3(C(3))), 32.07 (C(2″)), 25.71 (C(3′)), 19.40 (C(3″)), 17.53 (C(2′)), 13.97 (C(4″)); IR (CH_2Cl_2): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1285 (m), 1256 (w), 1177 (m), 1095 (m); TLC R_f 0.15 (hexane/Et_2O, 4/1); MS (FAB): 474 (30), 473 (100), 337 (40); $[\alpha]_D^{24} = +39.7$ (*c* 0.67, MeOH); Anal. Calcd for $C_{28}H_{44}N_2O_4$ (472.66): C, 71.15; H, 9.38; N, 5.93. Found: C, 71.63; H, 9.57; N, 6.00. HRMS (ESI, 70 eV): Calcd for $C_{28}H_{45}N_2O_4$, 473.3389. Found: 473.3384.

6.1.21. (*R*)-5-Methyl-1-(1-butoxy-2-dimethyl-2-phenylpropyl)pyridine *N*-oxide (*R*)-38. Following general procedure 1, pyridine (*R*)-**37** (1.16 g, 3.9 mmol) and *m*CPBA (1.01 g, 5.9 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (15 mL) and the mixture stirred overnight at rt. Work-up provided 1.44 g of white solid residue. Purification by silica gel column chromatography (CH_2Cl_2/MeOH, 20/1) provided the product (1.14 g, 92%) as a colorless oil. An analytically pure sample was obtained after bulb-to-bulb distillation. Data for (*R*)-**38**: bp: 180 °C ABT (0.05 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$): 8.08 (s, 1H, HC(6)), 7.43 (d, $J = 7.3$, 2H, HC(5′)), 7.28 (t, 2H, $J = 7.1$, HC(6′)), 7.19–7.22 (m, 1H, HC(7′)), 6.87 (d, $J = 8.0$, 1H, HC(3)), 6.67 (d, $J = 8.3$, 1H, HC(4)), 5.40 (s, 1H, HC(1′)), 3.05–3.15 (m, 2H, H_2C(8′)), 2.26 (s, 3H, H_3C(C(5))), 1.47 (s, 3H, H_3C(3′)), 1.45 (s, 3H, H_3C(3′)), 1.31–1.37 (m, 2H, H_2C(9′)), 1.15–1.22 (m, 2H, H_2C(10′)), 0.77 (t, $J = 7.3$, 3H, H_3C(11′)); ^{13}C NMR (100 MHz, $CDCl_3$): 148.70 (C(2)), 145.74 (C(6)), 139.23 (C(4′)), 134.54 (C(5)), 127.56 (C(3)), 127.30 (C(5′ or 6′)), 126.15 (C(5′ or 6′)), 125.93 (C(7′)), 125.36 (C(4)), 80.15 (C(1′)), 69.72 (C(8′)), 43.88 (C(2′)), 31.65 (CH_3(C(5)) or C(9′)), 26.53 (CH_3(C(5)) or C(9′)), 22.60 (C(10′)), 19.18 (C(3′)), 17.95 (C(3′)), 13.71 (C(11′)); IR (neat): 3090 (w), 3058 (w), 3034 (w), 2959 (s), 2931 (s), 2871 (s), 1612 (m), 1553 (m), 1499 (s), 1476 (s), 1448 (s), 1384 (s), 1366 (m), 1339 (m), 1285 (s), 1258 (s), 1212 (m), 1182 (s), 1093 (s), 1032 (m), 1093 (s), 1020 (m), 955 (m), 881 (w), 827 (m), 809 (m), 769 (m), 752 (w); TLC R_f 0.52 (CH_2Cl_2/MeOH, 20/1); MS (FAB): 315 (22), 314 (100), 298 (19), 240 (16), 122 (13), 119 (17); $[\alpha]_D^{24} = +93.8$ (*c* 1.15, EtOH); Anal. Calcd for $C_{20}H_{27}N_1O_2$ (313.44): C, 76.64; H, 8.68; N, 4.47. Found: C, 76.67; H, 8.69; N, 4.69.

6.1.22. (*P*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-butyloxy-2-methyl-2-phenylpropyl)-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-11. To a suspension of (*R*)-**38** (880 mg, 2.8 mmol) in Et_2O (3 mL) was added freshly prepared LiTMP solution (*n*-BuLi, 1.8 mL, 2.9 mmol, 1.04 equiv, and tetramethylpiperidine 500 μL, 2.9 mmol, 1.04 equiv) in THF (3 mL) at −73 °C. After being stirred for 16 h at −73 °C, a solution of iodine (369 mg, 1.5 mmol, 0.5 equiv) in THF (5 mL) was added dropwise over 5 min into the resulting deep-red solution at −73 °C. The mixture was further stirred at −73 °C for 1 h until the color of the mixture discharged and a second portion of iodine (370 mg, 1.5 mmol, 0.5 equiv) in THF (5 mL) was added into the flask. The cooling bath was immediately removed and the reaction mixture was brought up to rt over 40 min. During the warming period, the deep-red color reappeared. After being stirred at rt for 2 h, cold water (10 mL) was added into the flask, followed by saturated $NaHSO_3$ solution (10 mL). The mixture was transferred to a separatory funnel, diluted with NH_4OH solution (20 mL), and thoroughly extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The brownish residue was purified by silica gel column chromatography (pentane/ether, 2/1) to provide 1.35 g of the mixture of (*P*)-(*R*,*R*)-**11** and the by-product iodide (*R*)-**34d**. The iodide (164 mg, 27%) was removed

by recrystallization from pentane. From the mother liquor, (*P*)-(*R*,*R*)-**11** (523 mg, 61%) was obtained. An analytically pure sample was obtained after crystallization from hexane. Data for (*P*)-(*R*,*R*)-**11**: mp: 149–150.5 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 7.47 (dd, $J = 7.3$, 1.1, 4H, HC(5′)), 7.27 (t, $J = 7.3$, 4H, HC(6′)), 7.28 (t, $J = 7.0$, 2H, $J = 7.1$, HC(7′)), 7.09 (AB quartet, $J = 8.3$, 8H, HC(4) and HC(5)), 5.48 (s, 2H, HC(1′)), 3.06–3.22 (m, 4H, $H_2C(8')$), 2.05 (s, 6H, $H_3C(C(5))$), 1.40 (s, 6H, $H_3C(3')$), 1.36 (s, 6H, $H_3C(3')$), 1.29–1.33 (m, 4H, $H_2C(9')$), 1.15–1.20 (m, 4H, $H_2C(10')$), 0.77 (t, $J = 7.3$, 3H, $H_3C(11')$); ^{13}C NMR (100 MHz, $CDCl_3$): 149.08 (C(2)), 146.52 (C(6)), 142.62 (C(4′)), 134.92 (C(3)), 127.38 (C(5′ or 6′)), 127.30 (C(5′ or 6′)), 125.84 (C(7′)), 125.26 (C(4)), 80.38 (C(1′)), 69.91 (C(8′)), 44.02 (C(2′)), 31.79 (CH_3(C(5)) or C(9′)), 26.33 (CH_3(C(5)) or C(9′)), 22.21 (C(10′)), 19.20 (C(3′)), 17.57 (C(3′)), 13.81 (C(11′)); IR (KBr): 3090 (w), 3058 (w), 3023 (w), 2959 (s), 2932 (s), 2872 (s), 1740 (s), 1601 (m), 1497 (m), 1476 (s), 1446 (s), 1388 (s), 1369 (s), 1329 (s), 1269 (s), 1241 (s), 1096 (s), 1048 (s), 966 (w), 787 (m), 770 (m); TLC R_f 0.41 (hexane/EtOAc, 4/1); MS (FAB, 70 eV): 627 (11), 626 (44), 625 (100), 609 (19); $[\alpha]_D^{24} = +27.5$ (*c* 1.01, EtOH); Anal. Calcd for $C_{40}H_{52}N_2O_4$ (624.42): C, 76.94; H, 8.39; N, 4.49. Found: C, 76.64; H, 8.34; N, 4.57.

6.1.23. (*R*)-5-Methyl-1-(1-butyloxy-2,2-diethylbutyl)pyridine *N*-oxide (*R*)-43. Following general procedure 1, pyridine (*R*)-**42** (486 mg, 1.75 mmol) and *m*CPBA (450 mg, 2.63 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (10 mL) and the mixture stirred overnight at rt. Work-up provided 477 mg of white solid residue. Purification by silica gel column chromatography (CH_2Cl_2/MeOH, 20/1) provided the product (457 mg, 89%) as a colorless oil. An analytically pure sample was obtained after bulb-to-bulb distillation. Data for (*R*)-**43**: bp: 180 °C ABT (0.1 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$): 8.05 (s, 1H, HC(6)), 7.36 (d, $J = 8.1$, 1H, HC(3)), 7.03 (d, $J = 8.1$, 1H, HC(4)), 5.25 (s, 1H, HC(1′)), 3.05–3.23 (m, 2H, $H_2C(1'')$), 2.27 (s, 3H, $H_3C(C(5))$), 1.46–1.53 (m, 2H, $H_2C(2'')$), 1.44 (q, $J = 7.3$, 6H, $3 \times H_2C(3')$), 1.29–1.42 (m, 2H, $H_2C(3'')$), 0.85 (t, $J = 7.3$, 3H, $H_3C(4'')$), 0.82 (t, $J = 7.3$, 9H, $3 \times H_3C(4')$); ^{13}C NMR (100 MHz, $CDCl_3$): 149.79 (C(2)), 139.45 (C(6)), 134.02 (C(5)), 126.21 (C(3) or C(4)), 125.99 (C(3) or C(4)), 78.04 (C(1′)), 69.56 (C(1″)), 44.51 (C(2′)), 32.07 (C(2″)), 25.40 ($H_3C(C(5'))$), 19.41 (C(3′)), 17.94 (C(3″)), 13.83 (C(4″)), 8.39 (C(4′)): IR (neat): 2965 (s), 2934 (s), 2878 (s), 1613 (w), 1503 (m), 1456 (m), 1379 (s), 1339 (m), 1284 (s), 1252 (m), 1212 (w), 1189 (m), 1165 (m), 1114 (m), 1093 (s), 1051 (s), 953 (m), 880 (w); TLC R_f 0.36 (hexane/EtOAc, 3/1); MS (FAB): 294 (100); $[\alpha]_D^{24} = +46.2$ (*c* 0.59, MeOH); Anal. Calcd for $C_{18}H_{31}NO_2$ (293.44): C, 73.67; H, 10.65; N, 4.77. Found: C, 73.94; H, 10.98; N, 4.81.

6.1.24. (*P*)-(*R*,*R*)-3,3′-Dimethyl-6,6′-bis-(1-butyloxy-2,2-diethylbutyl)-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-12. To a suspension of (*R*)-**43** (360 mg, 1.23 mmol) in Et_2O (1.0 mL) was added freshly prepared LiTMP solution (1.60 M *n*-BuLi, 840 μL, 1.35 mmol, 1.1 equiv, and tetramethylpiperidine 230 μL, 1.35 mmol, 1.1 equiv) in THF (0.5 mL) at −73 °C. After being stirred for 16 h at −73 °C, a solution of iodine (340 mg, 1.35 mmol, 1.1 equiv) in THF (1.5 mL) was added dropwise over 10 min into the resulting deep-red solution at −73 °C. The mixture was further stirred at −73 °C for 1 h until the color of the mixture was discharged. The cooling bath was immediately removed and the reaction mixture brought up to rt over 30 min. During the warming period, the deep-red color reappeared. After being stirred at rt for 40 min, cold water (10 mL) was added into the flask, followed by satd $NaHSO_3$ solution (15 mL). The mixture was transferred to a separatory funnel, diluted with NH_4OH solution (50 mL), and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The brownish residue was purified by silica gel column chromatography (pentane/ether, 2/1) to provide 330 mg of a mixture of (*P*)-(*R*,*R*)-**12** and the by-product iodide. The iodide (34 mg, 5%) was removed by recrystallization from pentane. From the mother liquor, (*P*)-(*R*,*R*)-**12** (277 mg, 77%) was obtained. An analytically pure sample was obtained after crystallization from pentane. Data for (*P*)-(*R*,*R*)-**12**: mp: 112–113 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$); 7.45 (d, $J = 8.2$, 2H, HC(5)), 7.16 (d, $J = 8.4$, 2H, HC(4)), 5.32 (s, 2H, HC(1′)), 3.19–3.28 (m, 4H, $H_2C(1')$), 2.04 (s, 6H, $H_3C(C(3))$), 1.43–1.53 (m, 4H, $H_2C(2')$), 1.29–1.43 (m, 16H, $H_2C(3')$ and $H_2C(3'')$), 0.88 (t, $J = 7.5$, 6H, $(H_3C(4')_3)$), 0.81 (t, $J = 7.5$, 19H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 150.24 (C(6)), 142.99 (C(2)), 134.49 (C(3)), 126.02 (C(4) or C(5)), 125.87 (C(5) or C(4)), 77.73 (C(1″)), 69.98 (C(1′)), 44.84 (C(2″)), 32.0 (C(2′)), 25.19 (CH_3(C(3))), 19.45 (C(3″)), 17.58 (C(3′)), 13.94 (C(4′)), 8.49 (C(4″)); IR (KBr): 2957 (s), 2871 (m), 1613 (w), 1503 (w), 1478 (w), 1461 (w), 1383 (m), 1285 (m), 1256 (w), 1177 (m), 1095 (m); TLC R_f 0.65 (hexane/EtOAc, 4/1); MS (FAB): 585 (100), 569 (20); $[\alpha]_D^{24} = -30.7$ (*c* 1.34, MeOH); Anal. Calcd for $C_{30}H_{48}N_2O_4$ (584.88): C, 73.93; H, 10.34; N, 4.79. Found: C, 73.89; H, 10.46; N, 4.74.

6.1.25. (*R*)-5-Bromo-1-(1-butyloxy-2,2-dimethylpropyl)-pyridine *N*-oxide (*R*)-47. Following general procedure 1, pyridine (*R*)-**46** (2.43 g, 8.09 mmol) and *m*CPBA (1.79 g, 10.1 mmol, 1.25 equiv) were dissolved in CH_2Cl_2 (25 mL) and the mixture stirred overnight at rt. Work-up provided 2.52 g of a white solid residue. Purification by silica gel column chromatography (CH_2Cl_2/MeOH, 20/1) provided the product (2.45 g, 99%) as a colorless oil. An analytically pure sample was obtained after bulb-to-bulb distillation. Data for (*R*)-**47**: bp: 220 °C ABT (0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$): 8.34 (d, $J = 1.7$, 1H, HC(6)), 7.36 (dd, $J = 8.6$, 1.7, 1H, HC(4)), 7.28 (d, $J = 8.5$, 1H, HC(3)), 4.94 (s, 1H, HC(1′)), 3.16–3.29 (m, 2H, $H_2C(1'')$), 1.44–1.51 (m, 2H, $H_2C(2'')$), 1.29–1.36 (m, 2H, $H_2C(3'')$), 0.96 (s, 9H, $H_3C(3')$), 0.87 (t, $J = 7.3$, 3H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 151.43 (C(2)), 140.89 (C(6)), 127.73 (C(4)), 125.88 (C(3)), 118.20 (C(5)), 80.23 (C(1′)), 70.12 (C(1″)), 37.33 (C(2′)), 31.84 (C(2″)), 25.56 (C(3′)), 19.33 (C(3″)), 13.83 (C(4″)); IR (KBr): 3094 (w), 3036 (w), 2933 (s), 2871 (s), 1596 (m), 1532

(w), 1477 (s), 1370 (s), 1244 (s), 1094 (s), 901 (s); TLC R_f 0.18 (hexane/Et_2O, 3/1); MS (FAB): 318 (8), 316 (8), 244 (98), 242 (100); $[\alpha]_D^{24} = -27.3$ (*c* 0.22, MeOH); Anal. Cacld for $C_{14}H_{22}BrNO_2$ (316.23): C, 53.17; H, 7.01; N, 4.43. Found: C, 53.42; H, 7.19; N, 4.49.

6.1.26. (*P*)-(*R*,*R*)-3,3′-Dibromo-6,6′-bis-(1-butyloxy-2,2-dimethylpropyl)-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-13. Following general procedure 2, from (*R*)-**47** (948 mg, 3.0 mmol), 312 mg (33%) of the product (*P*)-(*R*,*R*)-**13** was obtained as a white solid after silica gel column chromatography (pentane/ether, 2/1). An analytically pure sample was obtained after crystallization from pentane. Data for (*P*)-(*R*,*R*)-**13**: mp: 175–179 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$): 7.26 (dd, $J = 8.6$, 1.7, 1H, HC(4)), 7.18 (d, $J = 8.5$, 1H, HC(5)), 4.92 (s, 1H, HC(1′)), 3.16–3.29 (m, 2H, $H_2C(1'')$), 1.44–1.51 (m, 2H, $H_2C(2'')$), 1.29–1.36 (m, 2H, $H_2C(3'')$), 0.96 (s, 9H, $H_3C(3')$), 0.87 (t, $J = 7.3$, 3H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 151.38 (C(6)), 128.15, 127.47, 127.41, 124.98, 82.54 (C(1′)), 70.48 (C(1″)), 37.74 (C(2′)), 32.10 (C(2″)), 25.97 (C(3′)), 19.59 (C(3″)), 14.09 (C(4″)); TLC R_f 0.32 (hexane/EtOAc, 5/1); MS (FAB): 634 (8), 633 (8), 632 (8), 631 (8), 244 (98), 242 (100); Opt. Rot.: $[\alpha]_D^{24} = +29.9$ (*c* 0.28, EtOH); HRMS (ESI): Calcd for $C_{28}H_{43}Br_2N_2O_4$, 629.1597. Found: 629.1590. Calcd for $C_{28}H_{42}Br_2N_2Na_1O_2$ 651.1410. Found: 651.1413.

6.1.27. (*R*)-3,5-Dimethyl-1-(1-butyloxy-2,2-dimethylpropyl)pyridine *N*-oxide (*R*)-53. Following general procedure 1, pyridine (*R*)-**52** (2.90 g, 11.8 mmol) and *m*CPBA (2.51 g, 14.2 mmol, 1.25 equiv) were dissolved in CH_2Cl_2 (25 mL) and the mixture stirred overnight at rt. Work-up provided 3.02 g of white solid residue. Purification by silica gel column chromatography (R_f 0.33, CH_2Cl_2/MeOH, 20/1) provided the product (2.77 g, 89%) as colorless oil. An analytically pure sample was obtained after bulb-to-bulb distillation. Data for (*R*)-**53**: bp 220 °C ABT (0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$): 7.97 (s, 1H, HC(6)), 6.84 (s, 1H, HC(4)), 5.50 (s, 1H, HC(1′)), 3.50 (t, $J = 8.3$, 2H, $H_2C(1'')$), 2.48 (s, 3H, $H_3C(3)$ or $H_3C(5)$), 2.21 (s, 3H, $H_3C(3)$ or $H_3C(5)$), 1.44–1.52 (m, 2H, $H_2C(2'')$), 1.29–1.36 (m, 2H, $H_2C(3'')$), 1.02 (s, 9H, $H_3C(3')$), 0.87 (t, $J = 7.3$, 3H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 147.58 (C(2)), 137.85 (C(6)), 136.62 (C(3) or C(5)), 133.24 (C(3) or C(5)), 130.87 (C(4)), 82.90 (C(1′)), 70.57 (C(1″)), 39.19 (C(2′)), 32.12 (C(2″)), 27.26 (C(3′)), 19.67, 19.46, 17.86, 14.13; IR (neat): 3094 (w), 3036 (w), 2933 (s), 2871 (s), 1596 (m), 1532 (w), 1477 (s), 1370 (s), 1244 (s), 1094 (s), 901 (s); TLC R_f 0.18 (Et_2O); MS (FAB): 266 (14), 265 (100); $[\alpha]_D^{24} = +31.7$ (*c* 0.37, EtOH); Anal. Calcd for $C_{16}H_{27}NO_{02}$ (265.39): C, 72.41; H, 10.25; N, 5.28. Found: C, 72.07; H, 10.38; N, 5.38.

6.1.28. (*P*)-(*R*,*R*)-3,3′,5,5′-Tetramethyl-6,6′-bis-(1-butyloxy-2,2-dimethylpropyl)-2,2′-bipyridine bis-*N*-oxide (*P*)-(*R*,*R*)-15. Following general procedure 2, using (*R*)-**53** (530 mg, 2.0 mmol), 228 mg of the product (*P*)-(*R*,*R*)-**15** (43%) was obtained as a white solid after silica gel column chromatography (pentane/ether, 2/1). An analytically pure sample was obtained after crystallization from hexane. Data for (*P*)-(*R*,*R*)-**15**: mp: 167–169 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 6.93 (s, 2H, HC(4)), 5.27 (s, 2H, HC(1′)), 3.28–3.37 (m, 4H, $H_2C(1'')$), 2.53 (s, 6H, $H_3C(3)$ or $H_3C(5)$), 1.97 (s, 6H, $H_3C(3)$ or $H_3C(5)$), 1.42–1.60 (m, 4H, $H_2C(2'')$), 1.29–1.40 (m, 4H, $H_2C(3'')$), 1.02 (s, 18H, $H_3C(3')$), 0.89 (t, $J = 7.3$, 3H, $H_3C(4'')$); ^{13}C NMR (100 MHz, $CDCl_3$): 150.56 (C(6)), 143.09 (C(2)), 134.61 (C(3) or C(5)), 126.93 (C(3) or C(5)), 123.63 (C(4)), 79.75 (C(1′)), 70.59 (C(1″)), 32.27 (C(2′)), 31.33 (C(2″)), 19.64, 19.57, 17.69, 16.73, 14.19; TLC R_f 0.33 (hexane/EtOAc, 6/1); IR (KBr): 3094 (w), 3036 (w), 2933 (s), 2871 (s), 1596 (m), 1532 (w), 1477 (s), 1370 (s), 1244 (s), 1094 (s), 901 (s); MS (FAB): 530 (18), 529 (100); $[\alpha]_D^{24} = +39.4$ (*c* 0.89, EtOH); HRMS (ESI): Calcd for $C_{32}H_{57}N_2O_4$, 529.4005. Found: 529.3997.

6.1.29. (*R*)-3-Methyl-(8-(1-butyloxy)-(5,6,7,8)-tetrahydro)-quinoline *N*-oxide (*R*)-57. Following general procedure 1, pyridine (*R*)-**56** (5.02 g, 22.9 mmol) and *m*CPBA (5.23 g, 29.2 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (50 mL) and the mixture stirred overnight at rt. Work-up provided 5.09 g of an oily residue. Purification by silica gel column chromatography (R_f 0.35, CH_2Cl_2/MeOH, 20/1) provided the product as colorless oil (5.20 g, 96%). An analytically pure sample was obtained after bulb-to-bulb distillation. Data for (*R*)-**57** bp: 180 °C ABT (0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$): 7.99 (d, $J = 0.4$, 1H, HC(2)), 6.80 (d, $J = 0.4$, 1H, HC(4)), 4.94 (t, $J = 4.7$, 1H, HC(8)), 3.70–3.89 (m, 2H, $H_2C(1')$), 2.57–2.81 (m, 2H, $H_2C(5)$), 2.22 (s, 3H, $H_3C(3)$), 1.91–2.03 (m, 2H, $H_2C(2')$), 1.72–1.77 (m, 2H, $H_2C(7)$), 1.52–1.67 (m, 2H, $H_2C(3')$), 1.31–1.41 (m, 2H, $H_2C(6)$), 0.90 (t, $J = 7.3$, 3H, $H_3C(4')$); ^{13}C NMR (100 MHz, $CDCl_3$) 143.43 (C(9)), 137.39 (C(2)), 136.20 (C(3) or C(10)), 134.27 (C(3) or C(10)), 127.33 (C(4)), 70.79 (C(8)), 67.53 (C(1′)), 32.29 (C(2′)), 27.95, 27.52, 19.43, 18.03, 16.55, 13.95; IR (neat): 3094 (w), 3036 (w), 2933 (s), 2871 (s), 1596 (m), 1532 (w), 1477 (s), 1370 (s), 1244 (s), 1094 (s), 901 (s); TLC R_f 0.23 (Et_2O/EtOH, 20/1): MS (FAB): 236 (100), 162 (60); $[\alpha]_D^{24} = +4.9$ (*c* 0.61, MeOH); Anal. Calcd for $C_{14}H_{21}NO_2$ (235.32): C, 71.46; H, 8.99; N, 5.95. Found: C, 71.23; H, 9.17; N, 6.06.

6.1.30. (*R*)-2-Iodo-3-methyl-(8-(1-butyloxy)-5,6,7,8-tetrahydro)quinoline (*R*)-58. To a suspension of (*R*)-**57** (990 mg, 6.0 mmol) in Et_2O (20 mL) was added freshly prepared LiTMP solution (*n*-BuLi, 1.56 M, 4.5 mL, 6.6 mmol, 1.1 equiv, and tetramethylpiperidine 940 μL, 6.6 mmol, 1.1 equiv) in THF (10 mL) at −73 °C. After being stirred for 16 h at −73 °C, a solution of iodine (756 mg, 3.0 mmol, 0.5 equiv) in THF (5 mL) was added dropwise over 10 min into the resulting deep-red solution at −73 °C. The mixture was further stirred at −73 °C for 1 h until the color of the mixture discharged and a second portion of iodine (756 mg, 3.0 mmol, 0.5 equiv) in THF (5 mL) was added into the flask. The cooling bath was immediately removed and the reaction mixture was brought up to rt over 40 min. During the warming period, the deep-red color was recharged. After being stirred at rt for 2 h, cold water

(10 mL) was added into the flask, followed by satd $NaHSO_3$ solution (10 mL). The mixture was transferred to a separatory funnel, diluted with NH_4OH solution (50 mL), and thoroughly extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The brownish residue was purified by silica gel column chromatography (pentane/ether, 2/1) to provide 1.32 g of mixture of dimeric products and the iodide (*R*)-**58**. The iodide (930 mg, 69%) was recrystallized from the pentane solution of this mixture. From the mother liquor, a mixture of two dimers (207 mg, 23%) was obtained. Data for (*R*)-**58**: mp: 106–109 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$); 6.83 (s, 1H, HC(4)), 4.92 (t, $J = 4.7$, 1H, HC(8)), 3.68–3.96 (m, 2H, $H_2C(1')$), 2.54–2.79 (m, 2H, $H_2C(5)$), 2.42 (s, 3H, $H_3C(3)$), 2.22–2.26 (m, 2H, $H_2C(2')$), 1.91–2.03 (m, 2H, $H_2C(7)$), 1.72–1.82 (m, 2H, $H_2C(3')$), 1.28–1.64 (m, 2H, $H_2C(6)$), 0.90 (t, $J = 7.3$, 3H, $H_3C(4')$); ^{13}C NMR (100 MHz, $CDCl_3$): 144.68 (C(9)), 140.64 (C(2)), 135.08 (C(3) or C(10)), 126.23 (C(3) or C(10)), 115.73 (C(4)), 71.03 (C(8)), 69.25 (C(1′)), 32.26 (C(2′)), 27.72, 27.65, 27.26, 19.40, 16.41, 13.94; IR (KBr): 3094 (w), 3036 (w), 2933 (s), 2871 (s), 1596 (m), 1532 (w), 1477 (s), 1370 (s), 1244 (s), 1094 (s), 901 (s); TLC R_f 0.35 (Et_2O): MS (ESI): 362 (40); $[\alpha]_D^{24} = -7.2$ (*c* 1.16, EtOH); Anal. Calcd for $C_{14}H_{20}INO_2$ (361.22): C, 46.55; H, 5.58; N, 3.88. Found: C, 46.83; H, 5.23; N, 3.86.

6.1.31. (*P*)- and (*M*)-(*R*,*R*)-3,3′-Dimethyl-(8,8′-bis-(1-butyloxy)-5,6,7,8-tetrahydro)bisquinoline bis-*N*-oxide 16a and 16b. A mixture of (*R*)-**58** (842 mg, 2.5 mmol) and copper (640 mg, 10 mmol, 4 equiv) in DMF (4 mL) was heated at 150 °C for 2 h. The suspension was diluted with Et_2O (40 mL) and was filtered off through Celite and the filtrate was concentrated under reduced pressure. The brownish residue was dissolved in CH_2Cl_2 (10 mL) and to this solution was added *m*CPBA (520 mg, 3.0 mmol). The mixture was stirred overnight at rt and then was washed with satd aq $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification of the brownish residue by silica gel column chromatography (diethyl ether) provided isomer (+)-**16a** (R_f 0.33, Et_2O, 420 mg, 52%) and isomer (−)-**16b** (R_f 0.29, Et_2O, 184 mg, 22%). An analytically pure sample of each isomer was obtained after recrystallization from hexane. Data for (+)-**16a**: mp: 144–146 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 6.89 (s, 1H, HC(4)), 4.86 (t, $J = 4.7$, 1H, HC(8)), 3.72–3.84 (m, 2H, $H_2C(1')$), 2.47–2.72 (m, 2H, $H_2C(5)$), 2.09 (s, 3H, $H_3C(3)$), 1.89–2.03 (m, 2H, $H_2C(2')$), 1.72–1.79 (m, 2H, $H_2C(7)$), 1.51–1.67 (m, 2H, $H_2C(3')$), 1.31–1.42 (m, 2H, $H_2C(6)$), 0.92 (t, $J = 7.3$, 3H, $H_3C(4')$); ^{13}C NMR (100 MHz, $CDCl_3$): 146.43 (C(9)), 143.39 (C(2)), 139.23 (C(3) or C(10)), 134.53 (C(3) or C(10)), 128.32 (C(4)), 77.74 (C(8)), 68.54 (C(1′)), 32.10 (C(2′)), 28.95, 28.55, 20.47, 19.31, 16.76, 14.22; IR (KBr): 3094 (w), 3036 (w), 2933 (s), 2871 (s), 1596 (m), 1532 (w), 1477 (s), 1370 (s), 1244 (s), 1094 (s), 901 (s); TLC R_f 0.33 (Et_2O); MS (FAB): 469 (13), 468 (100); $[\alpha]_D^{24} = +21.3$ (*c* 1.15, MeOH); Anal. Calcd for $C_{28}H_{40}N_2O_4$ (468.63): C, 71.76; H, 8.60; N, 5.98. Found: C, 71.64; H, 8.75; N, 6.00.

Data for (−)-**16b**: mp: 153–155 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 6.93 (s, 2H, HC(4)), 4.99 (s, 2H, HC(8)), 3.69–3.87 (m, 2H, $H_2C(1')$), 2.61–2.85 (m, 2H, $H_2C(5)$), 2.05 (s, 3H, $H_3C(3)$), 1.95–2.23 (m, 2H, $H_2C(2')$), 1.75–1.79 (m, 2H, $H_2C(7)$), 1.51–1.67 (m, 2H, $H_2C(3')$), 1.28–1.38 (m, 2H, $H_2C(6)$), 0.87 (t, $J = 7.3$, 3H, $H_3C(4')$); ^{13}C NMR (100 MHz, $CDCl_3$): 145.46 (C(9)), 141.43 (C(2)), 135.86 (C(3) or C(10)), 126.99 (C(3) or C(10)), 116.51 (C(4)), 71.82 (C(8)), 71.05 (C(1′)), 33.06 (C(2′)), 28.52, 28.43, 28.06, 20.20, 17.21, 14.74; TLC R_f 0.29 (Et_2O); MS (FAB): 469 (13), 468 (100); $[\alpha]_D^{24} = -8.9$ (*c* 3.19, MeOH); Anal. Calcd for $C_{28}H_{40}N_2O_4$ (468.63): C, 71.76; H, 8.60; N, 5.98. Found: C, 71.57; H, 8.74; N, 6.05.

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