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Chiral pyridine *N*-oxides: useful ligands for asymmetric catalysis

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Abstract—The synthesis and applications in asymmetric catalysis of chiral pyridine *N*-oxide derivatives is reviewed.

Contents

1. Introduction

The rational design and synthesis of novel homochiral molecules directed towards asymmetric synthesis or asymmetric molecular recognition is one of the most important goals in modern organic chemistry.[1] In this context, a great number of homochiral molecules containing amines, ethers and phosphines as electron-pair donors have been developed as asymmetric controllers.[2] Although it is well documented that amine *N*-oxides act as powerful electron-pair donors, providing suitable electronic environments for a central metal ion,[3] applications of this kind of chiral ligand have been reported only sparingly.[4] On the other hand, in the last few years there has been an increasing interest in the synthesis and use of related optically active pyridine *N*-oxides as chiral controllers for asymmetric reactions.[5] This report outlines the synthesis of a range of chiral non-racemic pyridine *N*-oxides and their utility in various enantioselective processes.

2. Applications in asymmetric homogeneous catalysis

2.1. Allylation of aldehydes with allylchlorosilanes

The enantioselective allylation[6] of aldehydes with allylchlorosilanes[7] (Scheme 1) is the reaction that has most exploited pyridine *N*-oxide derivatives as chiral catalysts. This stems from the consideration that the *N*-oxide functional group possesses a notable electron-pair donor property, and exhibits a significant nucleophilicity

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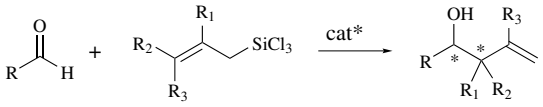


Scheme 1.

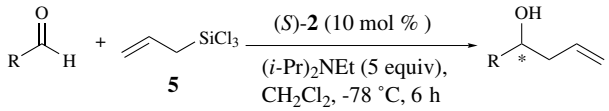
towards the silicon atom,[8] which in this way can form hypervalent silicates, which are involved as intermediates in the allylation reactions.

Nakajima et al. used the C_2-symmetric 2,2′-biquinoline *N*,*N*′-dioxide (*S*)-**2** and 1,1′-biisoquinoline *N*,*N*′-dioxide (*S*)-**4** as chiral catalysts in this reaction (Scheme 2).[9]

Racemic **2** was prepared by MCPBA oxidation of 3,3′-dimethyl-2,2′-biquinoline **1**, in turn readily obtained from anthranilic acid in three steps and then resolved via the hydrogen-bonding complex with (*S*)- or (*R*)-binaphthol (Scheme 2).[10]

Ligand (*S*)-**4** was initially obtained enantiomerically pure by preparative high performance liquid chromatography (HPLC) using a chiral column from racemic **4**,[11] which was prepared by *N*-oxidation of 1,1′-biisoquinoline **3**. Next, the racemic dioxide **4** was successfully resolved via complexation with (*R*)-binaphthol (Scheme 3).

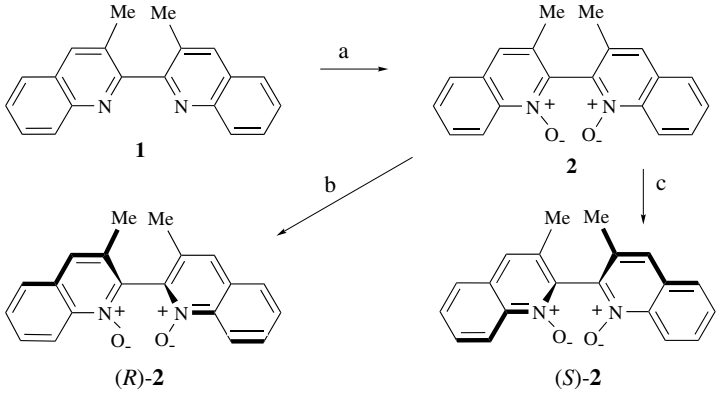
At the outset, the addition of allyltrichlorosilane **5** to benzaldehyde using 10 mol% of (*S*)-**4** was examined. The reaction (23 °C, 2 h) afforded 1-phenylbut-3-en-1-ol in 82% yield and 52% enantiomeric excess (ee) (Scheme 4, R = Ph). An improved yield (90%) and enantioselectivity (71% ee) was next found under the influence of (*S*)-**2**, wherein the *N*-oxide moieties were embedded within a chiral pocket created by the walls of the biaryl unit. After considerable experimentation based on this ligand, it was found that the reaction was notably accelerated (23 °C, 10 min) by the addition of 5 equiv of diisopropylethylamine with no loss of enantioselectivity (90% yield, 71% ee). The increase in the reaction rate made it possible to conduct the reaction at −78 °C, thereby enhancing the enantioselectivity up to 88% ee. Under these conditions a variety of aldehydes were assessed for the allylation with allyltrichlorosilane in the presence of (*S*)-**2** (Scheme 4). The results obtained are summarized in Table 1.



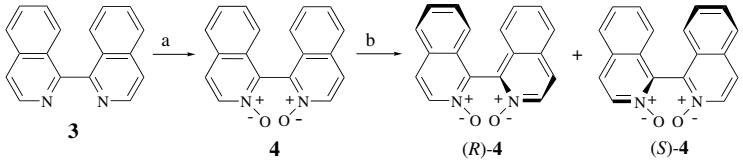
Scheme 4.

Table 1. Enantioselective allylation of different aldehydes (RCHO) with allyltrichlorosilane catalyzed by (*S*)-**2** (Scheme 4)

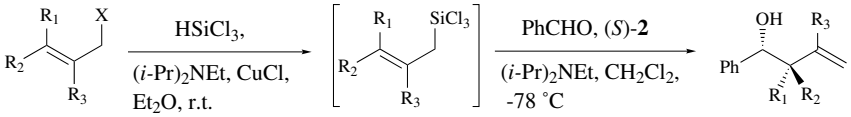
R	Yield (%)	Ee (%)	Configuration
Ph	85	88	*R*
4-$MeOC_6H_4$	91	92	*R*
4-$CF_3C_6H_4$	71	71	*R*
2-MeC_6H_4	70	90	*R*
1-Naphthyl	68	88	*R*
(*E*)-$C_7H_{15}CH{=}CH$	74	81	*R*
(*E*)-Ph—CH=CH–	87	80	*R*
$Ph(CH_2)_2$	30	7	*S*
c-Hex	27	28	*S*



Scheme 2. Reagents and conditions: (a) MCPBA; (b) (*S*)-binaphthol, then crystallization and column chromatography; (c) (*R*)-binaphthol, then crystallization and column chromatography.



Scheme 3. Reagents and conditions: (a) H_2O_2, AcOH, 80%; (b) enantiomeric separation by chiral HPLC or by complexation with (*R*)-binaphthol [for (*S*)-**4**].



6a-c **7a-c** **8a-c**

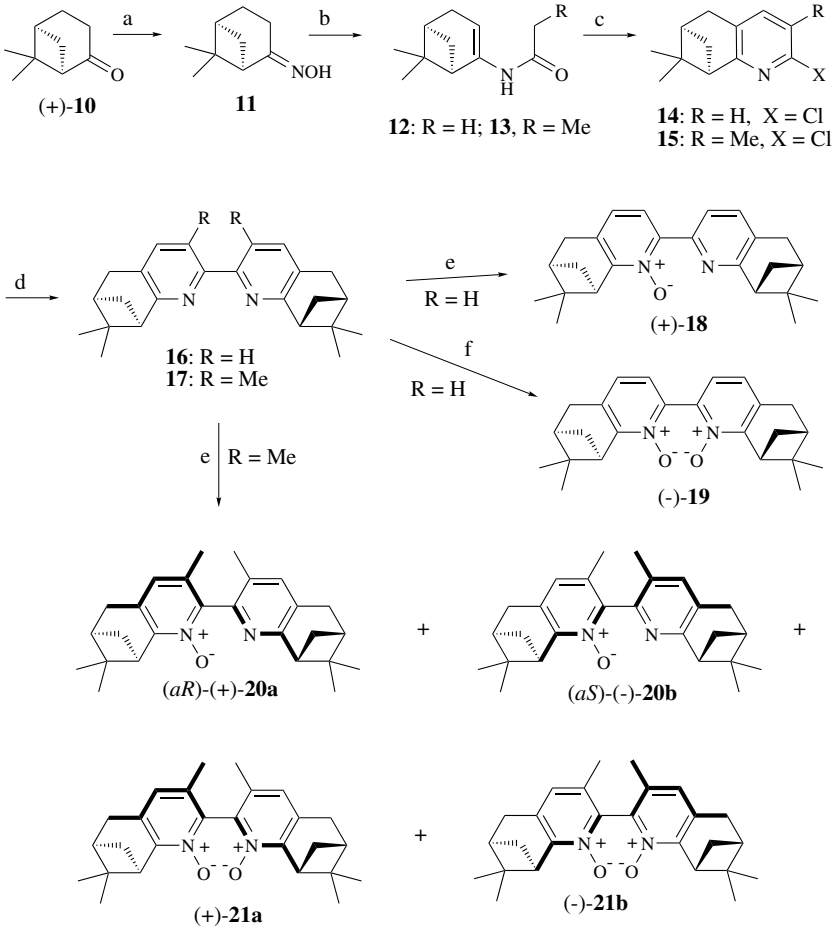
6a: $R_1 = R_2 = R_3 = H$, X = Cl,
6b: $R_1 = R_2 = H$, R_3 = Me, X = Cl,
6c: $R_1 = R_2 = H$, R_3 = Ph, X = Br,
6d: R_1 = Ph, $R_2 = R_3 = H$, X = Cl,
6e: $R_1 = R_3 = H$, R_2 = Me, X = Cl,

8a: $R_1 = R_2 = R_3 = H$, 95%, 87% ee
8b: $R_1 = R_2 = H$, R_3 = Me, 62%, 52% ee
8c: $R_1 = R_2 = H$, R_3 = Ph, 52%, 43% ee
8d: R_1 = Ph, $R_2 = R_3 = H$, 70%, 77% ee
8e: $R_1 = R_3 = H$, R_2 = Me, 66%, 86% ee, *syn:anti* = 3:97

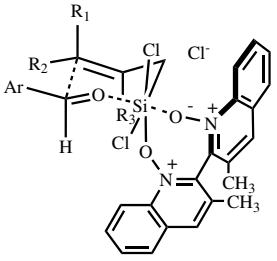
Scheme 5.

Next, the same group developed a modification of the *N*-oxide-catalyzed enantioselective addition of allyltrichlorosilanes to aldehydes, which entails the one-pot preparation of optically active homoallylic alcohols from allyl halides (Scheme 5).[12] According to this method, a number of allyltrichlorosilanes **7** (some examples are reported in Scheme 5) were generated in situ from allyl halides **6** and trichlorosilane in the presence of cuprous chloride and diisopropylethylamine. Without isolation of the allyltrichlorosilanes, benzaldehyde and (*S*)-**2** were introduced into the same flask, producing the corresponding homoallylic alcohols **8** with good to high enantioselectivities.

To establish the mechanistic profile of the amine *N*-oxide-promoted process, they then examined the allylation of benzaldehyde with (*E*)- and (*Z*)-crotyltrichlorosilanes. The obtained results suggested that the allylations proceeded via cyclic chair-like transition structures **9**, involving hypervalent silicates where one of the two *N*-oxides occupies an axial position.



Scheme 6. Reagents and conditions: (a) NH_2OH; (b) Fe, RCH_2CO_2H, $(RCH_2CO_2)O$; (c) DMF, $POCl_3$; (d) $NiCl_2$, Zn, Ph_3P; (e) MCPBA, CH_2Cl_2, 0 °C, 2 h; (f) MCPBA, CH_2Cl_2, rt, 24 h.

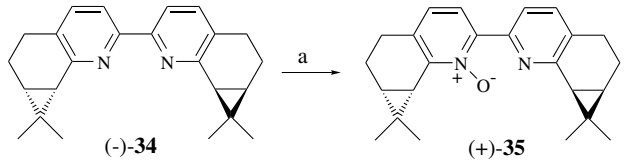


9

Malkov et al., and Kocovsky et al. used the chiral 2,2′-bipyridine *N*-monoxides **18**, **20a**,**b**, **30**–**33**, **35** and *N*,*N*′-dioxides **19**, **21a**,**b** (Schemes 6–8) derived from terpenes.[13,14]

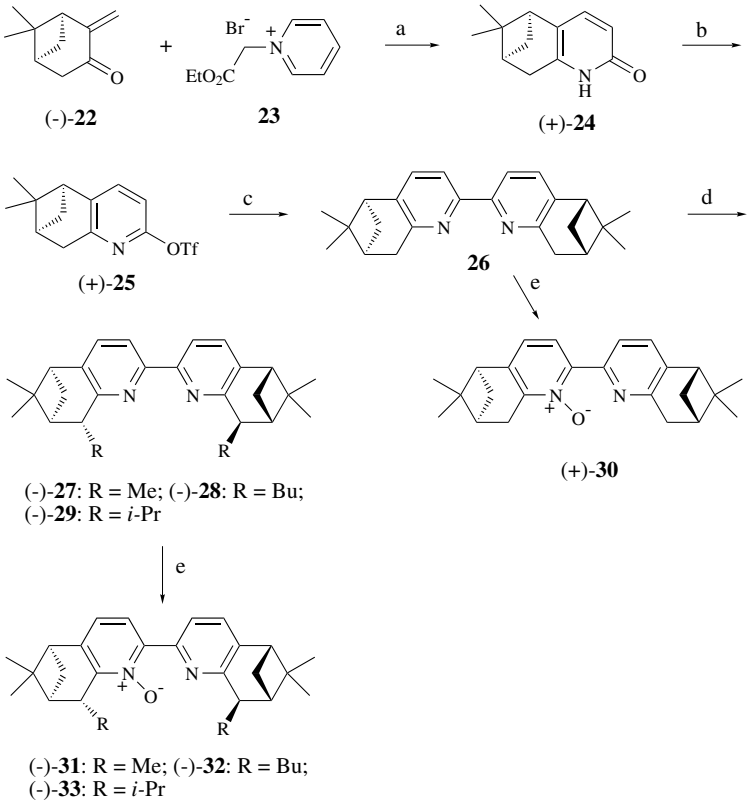
The synthesis of ligands **18** and **19** started from (+)-nopinone **10**, which was first converted into the oxime **11** and then into the enamide **12** by reductive acetylation (Scheme 6). Vilsmeier–Haack reaction on **12** afforded the chloropyridine derivative **14**. Finally, the Ni(0)-mediated coupling of the chloride **14** produced the bipyridine PINDY (+)-**16**,[15] whose *N*,*N*′-dioxide (−)-**19** was obtained by oxidation with MCPBA at room temperature for 24 h. Interestingly, when the oxidation was carried out at 0 °C for 45 min only the *N*-monoxide (+)-**18** was obtained.

To obtain the atropisomeric version of these oxides (Scheme 6), the compound (+)-**17**, differing from (+)-**16** by the presence of two methyl groups in the 3,3′-positions of the pyridine rings, was prepared using a protocol analogous to that developed for PINDY. In this case, propionic anhydride was employed instead of acetic anhydride in the reductive acylation of the oxime **11**. Unlike with PINDY, it was not possible to control the oxidation of **17** in favour of *N*-monoxide. Thus, the oxidation of **17** afforded two atropisomeric pairs of *N*-monoxides (+)-**20a** (17%), (−)-**20b** (30%) and *N*,*N*′-dioxides (+)-**21a** (14%), (−)-**21b** (24%). The compounds were separated by careful chromatography. The *N*-monoxides (+)-**20a** and (−)-**20b** were found to be configurationally unstable, in fact their isomerization occurred slowly at room temperature to reach a thermodynamic equilibrium (**20a**/**20b**, 1:2) within about three weeks in $CDCl_3$.



Scheme 8. Reagents and conditions: (a) MCPBA, CH_2Cl_2, 0 °C, 2 h.

The synthesis of ligands **30**–**33** commenced with the Kröhnke annulation between the pyridinium salt **23** and the α,β-unsaturated ketone **22**, derived from (+)-α-pinene (Scheme 7). The obtained pyridone **24** (43%) was converted into the triflate **25** (99%), which was dimerized via a Ni(0)-mediated coupling to give the bipyridine



Scheme 7. Reagents and conditions: (a) $AcONH_4$, AcOH, 80 °C; (b) Tf_2O; (c) $(Ph_3P)_2NiCl_2$, Zn, THF; (d) LDA, THF, −40 °C, 2 h then MeI or BuI or *i*-PrI; (e) MCPBA, CH_2Cl_2, 0 °C, 45 min.

26 (51%). The deprotonation of **26** with LDA, followed by alkylation with MeI, BuI or *i*-PrI gave the ligands **27**–**29** (56–99%).[3] Finally, controlled oxidation of these bipyridines afforded the corresponding *N*-monoxides **30**–**33** (43–67%).

The *N*-monoxide (+)-**35** was also prepared by oxidation of the bipyridine (−)-**34** (Scheme 8), available from (+)-2-carene in several steps.[15] However, the oxidation was not selective and the corresponding *N*,*N*′-dioxide was obtained too.

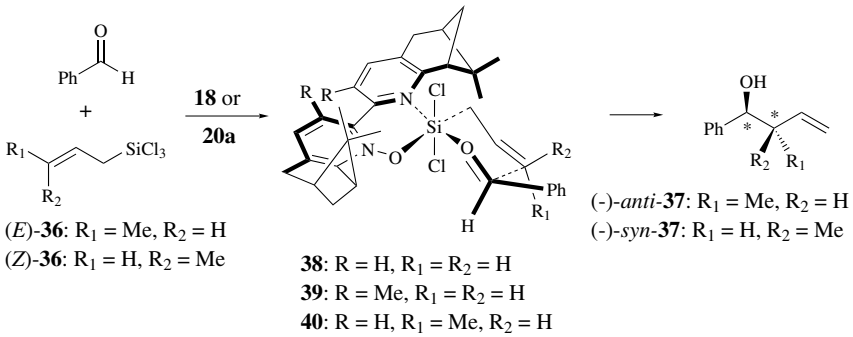
The addition of allyltrichlorosilane (1.1 equiv) to benzaldehyde, carried out with the *N*-monoxide (+)-**18** (10 mol%) as organocatalyst at −90 °C in the presence of Bu_4NI (1 equiv) produced the homoallylic alcohol in moderate yield (67%) and 92% ee (Table 2). Whereas ligand (+)-**18** proved to be a fairly efficient catalyst for the allylation of different aldehydes (see Table 2, for some examples), the corresponding *N*,*N*′-dioxide (−)-**19** showed to be considerably less selective (41% ee). The axially chiral ligand (*aS*)-(−)-**20b** gave the product of allylation with benzaldehyde in 82% ee. A considerable improvement of the enantioselectivity was obtained with the atropisomeric catalyst (*aR*)-(+)-**20a**, which gave the opposite enantiomeric allyl alcohol with 98% ee. Though **20a** was found to be the most enantioselective catalyst, its difficult preparation and its configurational instability precluded its use on large scale. Therefore, the *N*-monoxides **30**–**33** were assessed hoping to find a valuable alternative. Among these ligands, the *iso*-propyl derivative (−)-**33** was found to match the enantioselectivity of **20a** (96% ee with benzaldehyde). Also with electron-rich and electron-poor benzaldehyde derivatives, the enantioselectivity remained high (Table 2) and only marginal loss of enantioselectivity was observed when the reactions were carried out at −20 °C. By contrast, (+)-**35** exhibited very low enantioselectivity (22% ee).

To shed more light on the mechanism, the allylation of benzaldehyde with (*E*)-crotyltrichlorosilane (an 87/13 mixture of (*E*)/(*Z*)-isomers was used) was explored (Scheme 9). The catalyst (+)-**18** produced mainly *anti*-**37**

Table 2. Allylation of aldehydes (RCHO) with allyltrichlorosilane (Scheme 4)[a,b]

Entry	Catalyst	R	Solvent	Temperature (°C)	Time (h)	Yield (%)	Ee (%)	Configuration of **3**
1	(+)-**18**	Ph	CH_2Cl_2	−90	24	67	92	(*S*)-(−)
2	(+)-**18**	4-$MeOC_6H_4$	CH_2Cl_2	−60	24	68	87	(*S*)-(−)
3	(+)-**18**	4-$O_2NC_6H_4$	CH_2Cl_2	−60	24	58	65	(*S*)-(−)
4	(+)-**18**	PhCH=CH	CH_2Cl_2	−90	48	52	83	(*S*)-(−)
5	(+)-**18**	$PhCH_2CH_2$	CH_2Cl_2	−60	48	23	56	(*R*)-(+)
6	(+)-**18**	2-Furyl	CH_2Cl_2	−60	48	63	85	(*S*)-(−)
7	(+)-**18**	2-Thiophenyl	MeCN	−40	58	50	83	(*S*)-(−)
8	(−)-**19**	Ph	CH_2Cl_2	−90	24	67	92	(*S*)-(−)
9	(+)-**20a**	Ph	CH_2Cl_2	−60	12	72	98	(*S*)-(−)
10	(−)-**20b**	Ph	CH_2Cl_2	−60	24	67	82	(*R*)-(+)
11	(+)-**21a**	Ph	CH_2Cl_2	−60	24	52	14	(*R*)-(+)
12	(−)-**21b**	Ph	CH_2Cl_2	−60	24	57	10	(*S*)-(−)
13	(+)-**30**	Ph	CH_2Cl_2	−90	18	42	76	(*S*)-(−)
14	(−)-**31**	Ph	CH_2Cl_2	−60	18	75	88	(*S*)-(−)
15	(−)-**32**	Ph	CH_2Cl_2	−60	18	72	84	(*S*)-(−)
16	(−)-**33**	Ph	MeCN	−40	18	75	96	(*S*)-(−)
17	(−)-**33**	4-$MeOC_6H_4$	MeCN	−40	18	41	91	(*S*)-(−)
18	(−)-**33**	4-$CF_3C_6H_4$	MeCN	−40	18	88	96	(*S*)-(−)
19	(−)-**33**	2-Naphthyl	MeCN	−40	18	73	95	(*S*)-(−)
20	(−)-**33**	PhCH=CH	MeCN	−60	18	25	96	(*S*)-(−)
21	(+)-**35**	Ph	CH_2Cl_2	−60	24	90	22	(*S*)-(+)

[a] Only representative examples are reported; for further examples, see Refs. 13,14.
[b] The best stereochemical result obtained with each aldehyde is reported.



(*E*)-**36**: R_1 = Me, R_2 = H
(*Z*)-**36**: R_1 = H, R_2 = Me

38: R = H, R_1 = R_2 = H
39: R = Me, R_1 = R_2 = H
40: R = H, R_1 = Me, R_2 = H

(-)-*anti*-**37**: R_1 = Me, R_2 = H
(-)-*syn*-**37**: R_1 = H, R_2 = Me

Scheme 9.

Table 3. Allylation of benzaldehyde with (*E*)- and (*Z*)-crotyltrichlorosilane **36** (Scheme 9)

Entry	Catalyst	Crotyl	Solvent	Temperature (°C)	Time (h)	Yield (%)	*anti*/*syn* (% Ee)	Configuration of **37**
1	(+)-**18**	(*E*)-**36**[a]	CH_2Cl_2	−60	24	54	93 (87):7	(1*S*)-(−)
2	(−)-**33**	(*E*)-**36**[a]	CH_2Cl_2	−60	18	27	93 (⩾99): 7	(1*S*)-(−)
3	(−)-**33**	(*Z*)-**36**[b]	MeCN	−40	18	37	10:90 (87)	(1*S*)-(−)

[a] An 87/13 mixture of (*E*)/(*Z*)-isomers was used.
[b] Pure (*Z*)-isomer was used.

(Table 3, entry 1) and (−)-**33** behaved in a similar way, producing the *anti*-isomer practically enantiopure (entry 2). The (*Z*)-crotyltrichlorosilane **36** reacted much more slowly than its (*E*)-isomer and afforded mainly *syn*-**37** (entry 3). The discrepancy between the composition of the starting crotyl derivate and the *anti*/*syn* ratio of the product indicates that the reaction of (*E*)-**36** must be kinetically preferred over that of (*Z*)-**36**, which is confirmed by the slower reaction of pure (*Z*)-**36** (entry 3).

The high preference for the formation of *anti*-**37** from (*E*)-**36** and *syn*-**37** from (*Z*)-**36** is compatible with the generally accepted mechanism that involves a cyclic transition state, where the incoming aldehyde is coordinated to the Lewis-acidic site of silicon (Scheme 9) and the Lewis-base *N*-oxide oxygen is positioned *trans* to allylic group to enhance its nucleophilicity. Assuming chelation to the nitrogen of the second pyridine ring, the structures **38**–**40** represents the transition states, which are compatible with both absolute and relative stereochemistry of the allylation.

Hayashi et al. reported the synthesis of axially chiral 2,2′-bipyridine *N*,*N*′-dioxides (*S*)-**47a**–**d**, (*R*)-**48a**–**d** and (*R*)-**49** and their application in the allylation of aldehydes with allylsilanes.[16,17] These ligands were obtained by a new method (Scheme 10). Thus, the bipyridinediols **42a**–**d**, easily obtained from the substituted phenanthrolines **41a**–**d**, were coupled with (*R*)-2,2′-bis(chlorocarbonyl)-1,1′-binaphthalene in the presence of Et_3N to give in high yield cyclic diesters, which consist of a mixture of diastereomeric isomers (R_{nap},S_{pyr})-**43a**–**d** and (R_{nap},R_{pyr})-**44a**–**d** in a ratio of over 5:1 (configurations were determined by X-ray structure analysis). Isomerically pure (R_{nap},S_{pyr})-**43a**–**d**, which are the kinetic products, were obtained by chromatography on silica gel followed by GPC purification. An interesting epimerization was observed when the crude mixture of the diesters was heated in refluxing toluene or stirred at room temperature in toluene containing trifluoroacetic acid. The thermodynamically more stable diastereomers (R_{nap},R_{pyr})-**44a**–**d** were obtained as single isomers. Oxidation of the bipyridines **43** and **44** with MCPBA, followed by alkaline hydrolysis, gave the enantiomerically pure bipyridines (*S*)-**47a**–**d** and (*R*)-**48a**–**d**, whose axial chirality is now fixed by the formation of *N*,*N*′-dioxides. From (*R*)-**48a**, the methylether (*R*)-**49** was prepared in the conventional way.

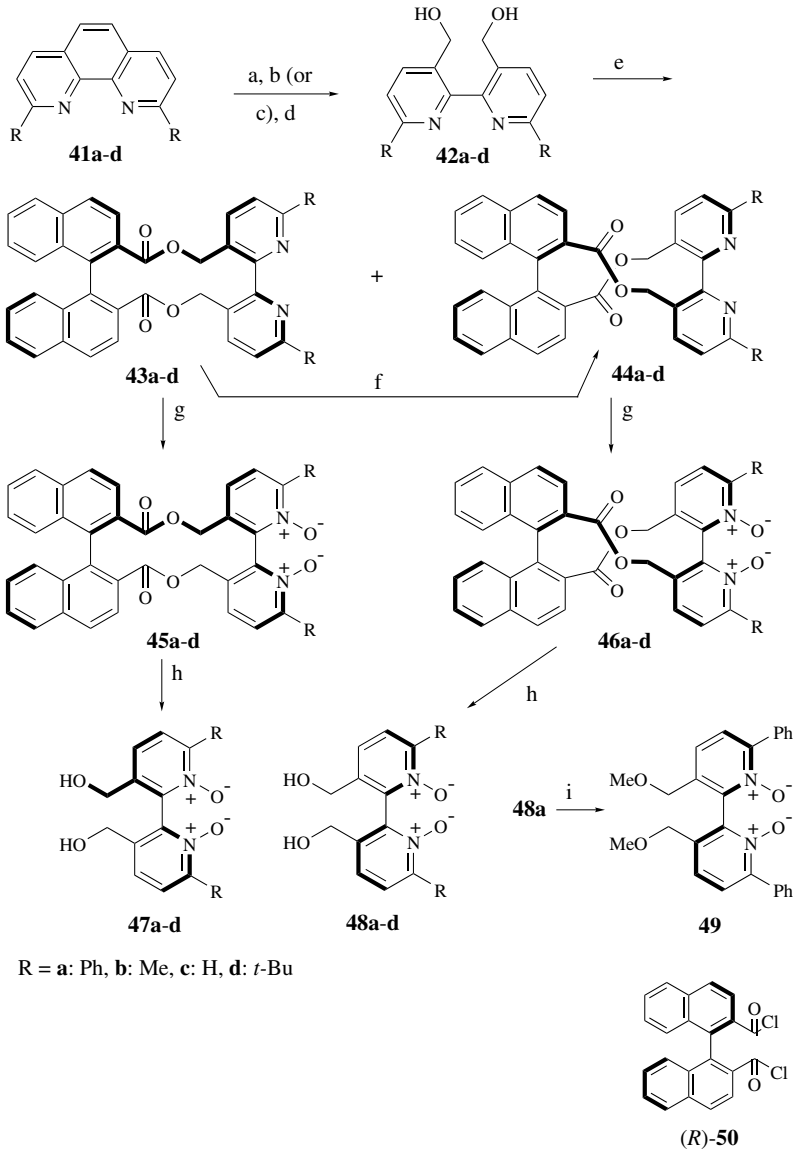
Among the *N*,*N*′-dioxides **48a**–**d**, (*R*)-**48a** was found to possess the highest catalytic activity and enantioselectivity for the asymmetric allylation of aromatic aldehydes with allyltrichlorosilane. Interestingly, the reactions carried out in acetonitrile at −45 °C were completed within 2.5 h even in the presence of only 0.1 mol % of the catalyst. The π–π stacking between the phenyl group on (*R*)-**48a** and the aromatic ring of the aldehyde in the transition state probably enhances the catalytic activity as well as the enantioselectivity.

The use of (*R*)-**48a** in the allylation of aromatic aldehydes, substituted with electron-donating and withdrawing groups, gave the corresponding homoallyl alcohols in high yields (86–94%). The highest enantioselectivities (up to 98% ee) were observed with aldehydes bearing electron-donating groups (4-$MeOC_6H_4CHO$, 96%, 94% ee; 3,4-$(MeO)_2C_6H_3CHO$, 95%, 98% ee; 4-*n*-BuC_6H_4CHO, 93%, 94% ee; 4-*t*-BuC_6H_4CHO, 93%, 89% ee; 4-MeC_6H_4CHO, 94%, 89% ee; PhCHO, 95%, 84% ee; 1-NapCHO, 90%, 81%; 2-$MeOC_6H_4CHO$, 93%, 76% ee; 4-$CF_3C_6H_4CHO$, 83, 56% ee; (*E*)-PhCH=CHCHO, 95%, 60% ee). Ligands **48b**–**c** afforded much poorer results, whereas no reaction occurred with **48d**.

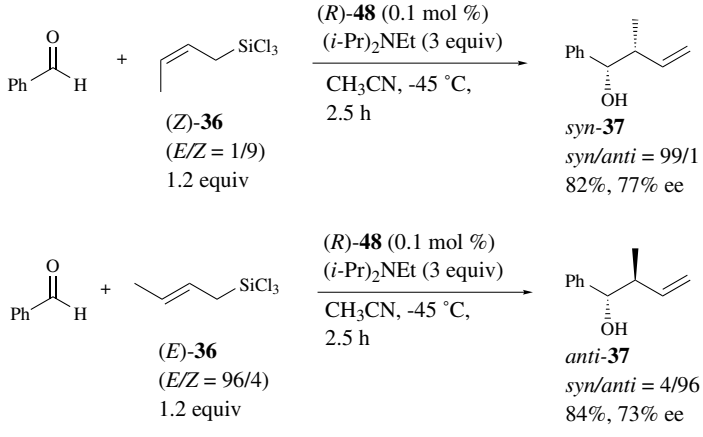
Crotylation catalyzed by (*R*)-**48** gave only γ-allylated homoallyl alcohol, whose relative configuration was *syn* from (*Z*)-crotyltrichlorosilane while it was *anti* from (*E*)-crotyltrichlorosilane, both in perfect regio- and diastereoselectivity (Scheme 11). These results support the mechanism, which entails the attachment of the bidentate *N*-oxide to the silicon atom to generate a pentacoordinate cationic silicate, which as Lewis acid then actives the carbonyl moiety of aldehyde and the nucleophilic attack to carbonyl carbon takes place at the γ-position of the allyl group via six-membered cyclic chair-like transition structures to give the corresponding homoallyl alcohols.

Malkov et al., and Kocovsky et al. prepared optically active *N*-monoxides from pyridine and isoquinoline that were then used in the enantioselective allylation of aldehydes with allylchlorosilanes.[18,19] These ligands were prepared to demonstrate that the presence of two donor atoms in the ligand (such as 2,2′-bipyridine *N*-mono- and *N*,*N*′-dioxides) is not a prerequisite for a good asymmetric induction.

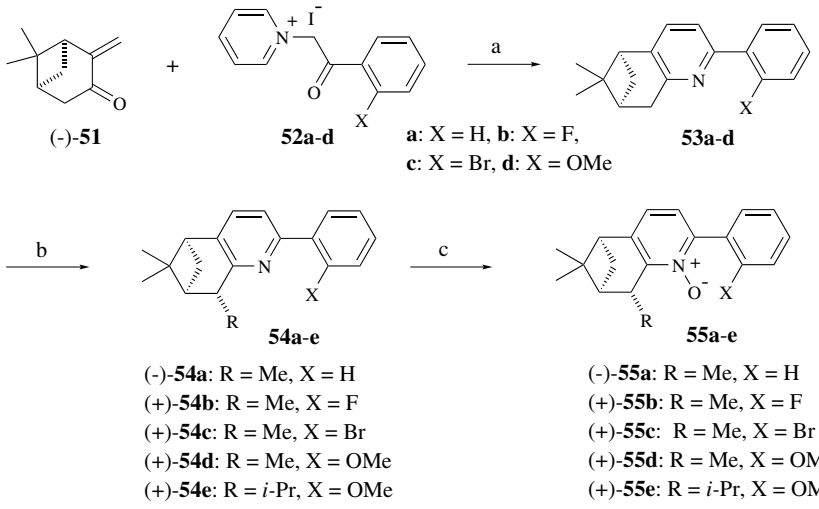
The pyridine *N*-oxides **55a**–**e**[18] (Scheme 12) were initially prepared from (−)-pinocarvone **51**, which by condensation with the Kröhnke salts **52a**–**d** led to the respective pyridine derivatives **53a**–**d** (40–83%). Deprotonation of these pyridines in the benzylic position followed by alkylation with MeI afforded the monomethyl derivates **54a**–**d** (68–98%). Analogously, by alkylation of **53d** with *i*-PrI, the isopropyl analogue **54e** was produced (68%). The *N*,*N*′-dioxides **55a**–**e** were finally obtained by oxidation of **54a**–**e** with MCPBA at room temperature for 4 h (64–85%).



Scheme 10. Reagents and conditions: (a) $KMnO_4$, $NaIO_4$; (b) CH_2N_2; (c) $SOCl_2$ then MeOH, Et_3N; (d) $LiAlH_4$, THF; (e) *R*-**50**, Et_3N, $CHCl_3$; (f) PhMe, reflux or CF_3COOH, PhMe; (g) MCPBA, CH_2Cl_2; (h) 6 N NaOH, MeOH; (i) NaH, MeI.



Scheme 11.



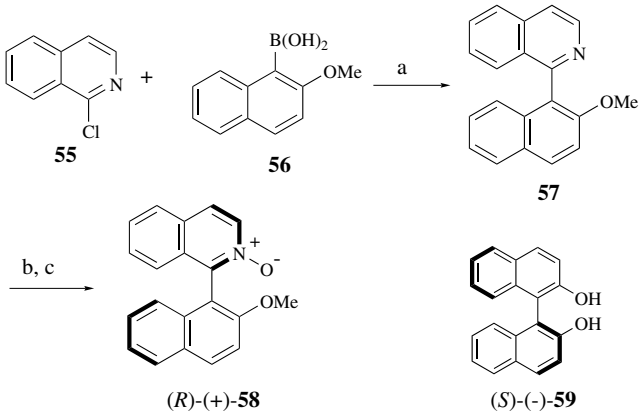
Scheme 12. Reagents and conditions: (a) $AcONH_4$, AcOH, 115 °C, overnight; (b) LDA, THF, −40 °C, 2 h then MeI or *i*-PrI; (c) MCPBA, CH_2Cl_2, rt, 4 h.

The addition of allyltrichlorosilane to benzaldehyde, carried out in the presence of **55a**–**e** and Bu_4NI at −60 °C for 18 h, produced the homoallylic alcohol in low to moderate yields (15–66%) and enantioselectivities (7–68% ee). The stereoselectivity increased on passing from *N*-oxides bearing electron withdrawing groups on the phenyl subunit (**55b**: 16% ee or **55c**: 7% ee) to those with electron donating groups (**55d**: 68% ee or **55e**: 67% ee). The latter results seem to indicate the involvement of silicon coordination by the methoxy group as a significant factor in the reaction course. However, the relatively high asymmetric induction in the case of the unsubstituted phenyl derivative **55a** (41% ee), in conjunction of the very low induction by **55b**,**c** suggests that the electronic properties of the phenyl group also play a role, presumably via a favourable π-stacking of the electron rich aryl **55a**,**e** with the incoming electron-poor aldehyde.

These findings suggested to Malkov et al., Kocovsky et al. that if the catalyst contains an electron-rich aromatic system, such as the *o*-methoxy-phenyl group in **55a**,**e**, it should be most effective with electron-poor aromatic aldehydes (i.e., with electron-withdrawing substituents) and vice versa. In line with this hypothesis the isoquinoline *N*-oxide derivative (*R*)-**58** was chosen as a candidate catalyst.

This ligand was synthesized as depicted in Scheme 13.[19] Coupling of 1-chloroisoquinoline **55** with the boronic acid **56** afforded the biaryl derivative **57** (95%), which by treatment with MCPBA provided the racemic *N*-oxide (±)-**58**. Resolution of (±)-**58** was obtained by co-crystallization with (*S*)-binol **59**, followed by a chromatographic separation of (+)-**58** from (*S*)-binol **59**.

The addition of allyltrichlorosilane (1 equiv) to a number of aromatic and heteroaromatic aldehydes (1.1 equiv) was carried out in the presence of (*R*)-**58** (5 mol %) and $(i\text{-Pr})_2NEt$ (1 equiv) at −40 °C in CH_2Cl_2 (Table 4).[19] Electron-rich aldehydes gave almost racemic products in good yields; by contrast, the introduction of



Scheme 13. Reagents and conditions: (a) $[(Ph_3P)_4Pd]$, Cs_2CO_3; DME, reflux, overnight; (b) MCPBA, CH_2Cl_2, rt, 2 h; (c) (*S*)-(−)-**59**, resolution.

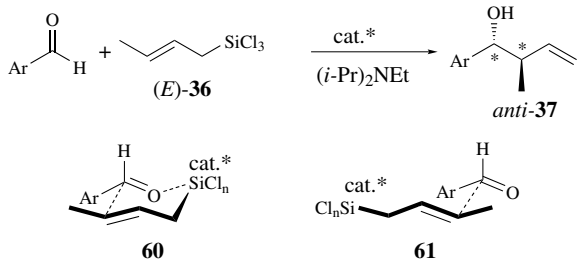
electron-withdrawing substituents into the *p*-position of benzaldehyde, resulted in a dramatic increase in both reactivity and enantioselectivity. The highest enantiomeric excess (96%) and yield (85%) was obtained with the 4-(trifluoromethyl)benzaldehyde.

Table 4. Enantioselective allylation of different aldehydes (RCHO) with allyltrichlorosilane catalyzed by (*R*)-**58**[a,b]

R	Time (h)	Yield (%)	Ee (%)
Ph	2	60	87
Cinnamyl	12	86	51
2-Furyl	12	68	5
4-Pyridyl	12	Trace	—
2-Thiophenyl	12	59	6
4-$MeOC_6H_4$	12	70	12
4-$O_2NC_6H_4$	2	73	89
4-ClC_6H_4	2	65	93
4-FC_6H_4	2	79	91
4-$CF_3C_6H_4$	2	85	96

[a] Only representative examples are reported; for further examples, see Ref. 19.

[b] The best stereochemical result obtained with each aldehyde is reported.



Scheme 14.

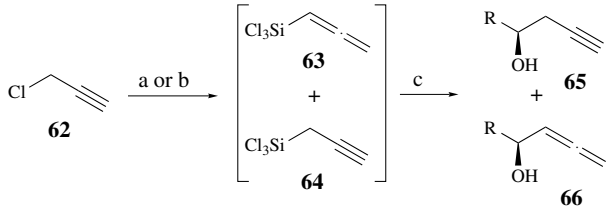
The observed data were fully compatible with the original hypothesis of arene–arene interaction of the catalyst with the incoming aldehyde. To shed more light on the mechanism, the allylation of *E*-crotyltrichlorosilane was examined (Scheme 14). With pindox **18** as the catalyst, the reaction produced mainly *anti*-**37** (Table 5, entry 1), which is compatible with the cyclic transition state **60** (Scheme 14). By contrast, a 2:1 *anti*/*syn* mixture was produced in the presence of **58**, suggesting a participation of the open-chain transition state **62**. In general, with **58** the cyclic transition state **60** is more favoured when arene–arene interactions are minimal as in the case of electron-rich aldehydes whose carbonyl oxygen are more prone to coordinate with silicon. By contrast, the transition state **60** is less favoured when arene–arene interactions operate as with electron-poor aldehydes, which are less suitable for coordination with silicon.

2.2. Addition of propargyl and allenylchlorosilane to aldehydes

Nakajima et al.[20] described the first examples of the selective preparation of optically active homopropargylic and allenic alcohols by the chiral *N*-oxide-catalyzed reaction of aldehydes with propargyltrichlorosilane or allenyltrichlorosilane, prepared in situ from propargyl chloride (Scheme 15). Two procedures (A and B), that substantially differ by the use of nickel bis(acetylacetate) or CuCl as the catalysts for the silylation of propargyl chloride, were followed. Method A afforded preferentially the allenyltrichlorosilane **63** (**63**/**64** = >30:1), which by treatment with benzaldehyde, in the presence of the chiral *N*-oxide (*S*)-**2** at −78 °C, provided the corresponding optically active homopropargylic alcohol **65** (**65**/**66** = >30:1) with 52% ee. On the other hand, Method B gave preferentially propargyltrichlorosilane **64** (**63**/**64** = 1:15), which afforded the chiral allenic alcohol **66** (**65**/**66** = 1:15) in 62% ee. Both methods afforded similar results with aromatic aldehydes, but lower reactivities and enantioselectivities with the aliphatic aldehyde hydrocinnamaldehyde (Table 6).

2.3. Conjugate addition of thiols to cyclic enones and enals

Nakajima et al. have recently reported the enantioselective conjugate addition of thiols to cyclic enones and enals catalyzed by chiral 2,2′-biquinoline *N*,*N*′-dioxide (*S*)-**2**-cadmium iodide complex (Scheme 16).[21,22]



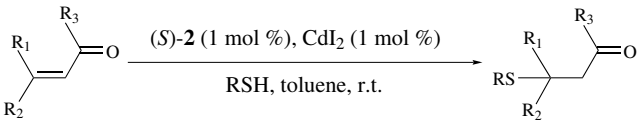
Scheme 15. Reagents and conditions: (a) method A, $HSiCl_3$ (2 equiv), $(i\text{-Pr})_2NEt$ (5 equiv), Ni-bis(acetylacetate) (5 mol%), THF, rt; (b) method B, $HSiCl_3$ (2 equiv), $(i\text{-Pr})_2$ NEt (5 equiv), CuCl (5 mol%) Et_2O/EtCN (10:1), rt; (c) RCHO, (*S*)-**2** (20 mol%), CH_2Cl_2, −78 °C, 6 h.

Table 5. Allylation of aldehydes (ArCHO) with (*E*)-crotyltrichlorosilane (Scheme 14)

Entry	Ar	Catalyst	Solvent	Yield (%)	*anti*/*syn*	Ee (%) *anti*, *syn*
1	Ph	(+)-**18**	CH_2Cl_2	54	93:7	87
2	Ph	(+)-**58**	CH_2Cl_2	70	68:32	65, 78
3	Ph	(+)-**58**	MeCN	51	76:24	56, 60
4	4-$MeOC_6H_4$	(+)-**58**	MeCN	53	82:18	50, 37
5	4-$CF_3C_6H_4$	(+)-**58**	CH_2Cl_2	76	70:30	92, 95
6	4-$CF_3C_6H_4$	(+)-**58**	MeCN	62	60:40	80, 84

Table 6. Selective synthesis of optically active allenylic and homopropargylic alcohols by addition of propargyl and allenyltrichlorosilane to aldehydes (RCHO) catalyzed by (*S*)-**2** (Scheme 15)

R	Method	Adduct [yield (%)]	**65**/**66** ratio	Ee (%)	Configuration
Ph	A	**55a** [65]	>30:1	78	*R*
4-$MeOC_6H_4$		**55b** [62]	>30:1	58	*R*
4-ClC_6H_4		**55c** [49]	>30:1	24	*R*
$PhCH_2CH_2$		**55d** [35]	>30:1	29	*R*
Ph	B	**66a** [72]	1:15	78	*R*
4-$MeOC_6H_4$		**66b** [76]	1:9	58	*R*
4-ClC_6H_4		**66c** [48]	1:9	24	*R*
$PhCH_2CH_2$		**66d** [44]	1:10	29	*R*



Scheme 16.

They initially examined the conjugate addition of thiophenol to 2-cyclohexen-1-one using various metal salts ($CuCl$, Zn_2Cl_2, $PdCl_2$, $AgCl$, $SnCl_2$, $HgCl$, $BiCl_3$, $CdCl_2$, CBr_2, CdI_2) in the presence of (*S*)-**2**. Among various metal chlorides surveyed, the use of cadmium chloride yielded the corresponding sulfides quantitatively with 30% ee. Further investigation revealed that 1 mol% of the complex, formed from an equimolar amount of cadmium iodide and (*S*)-**2** in toluene at room temperature is sufficient for optimum enantioselectivity. Table 7 summarizes the conjugate addition of various thiols to 2-cyclohexen-1-one under these optimized conditions.

The scope of the acceptor in the conjugate addition was also investigated. Slight modification of the substrate strongly influenced the enantioselectivity. With PhSH 2-cyclohepten-1-one gave an enantioselectivity (61% ee) comparable to that of 2-cyclohexen-1-one (78% ee), while 2-cyclopenten-1-one demonstrated low selectivity (21% ee). Introduction of a substituent into the 3- or 4-position of cyclohexanone resulted in decline in both chemical yield and enantioselectivity, probably for steric reasons. Finally, the addition of thiophenol to conjugated acyclic ketones was unsuccessful, while reaction with conjugated acyclic aldehydes afforded the corresponding sulfides in high yields and with enantioselectivities up to 70% ee. Thus, mildness of the reaction conditions allowed the enantioselective conjugate addition of thiols to enals, a reaction never previously reported due to the lability of aldehydes.

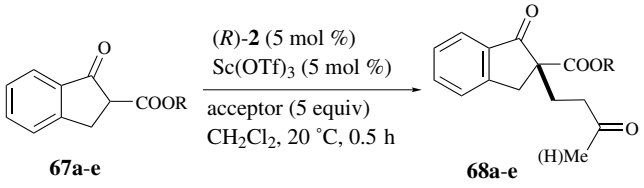
Table 7. Enantioselective conjugate addition of thiols (RSH) to 2-cyclohexen-1-one catalyzed by (*S*)-**2**-CdI_2 complex

R	Time (h)	Yield (%)	Ee (%)
Ph	6	96	78
2-MeC_6H_4	24	28	29
2,6-$Me_2C_6H_3$	48	8	33
4-MeC_6H_4	12	74	29
4-*t*BuC_6H_4	12	78	40
4-ClC_6H_4	3	98	24
4-$MeOC_6H_4$	6	91	58
$PhCH_2$	12	48	40

2.4. Michael addition of β-keto esters to methyl vinyl ketone

Metal complexes containing the chiral biquinoline *N*,*N*′-dioxide (*R*)-**2** have been applied by Nakajima et al. to catalytic enantioselective Michael additions, which are fundamental carbon–carbon bond formation reactions in organic synthesis, because the products are versatile chiral building blocks.[23]

Initially, no Michael adduct was obtained in an attempted Michael addition of dimethyl malonate to cyclohexenone employing the (*R*)-**2**-CdI_2 complex.[24] On the other hand, the Michael addition of methyl 1-oxoindan-2-carboxylate **67a** to methyl vinyl ketone (Scheme 17) with the same complex proceeded smoothly (75%), but the enantiomeric excess (13%) of the adduct was low.



67a-e **68a-e**

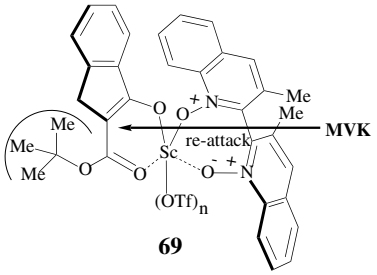
R = **a**: Me, **b**: $PhCH_2$, **c**: *i*-Pr, **d**: $(i\text{-Pr})_2CH$, **e**: *t*-Bu

Scheme 17.

After screening a number of complexes prepared in situ from (*R*)-**2** and various metal salts (CdI_2, $Yb(OTf)_3$, $Hf(OTf)_4$, $Sc(OTf)_3$ and $ScCl_3$), it was found that the 1:1 complex of (*R*)-**2** and scandium trifluoromethanesulfonate (5 mol%) in CH_2Cl_2 at room temperature catalyzed the Michael addition of **67a** to generate the adduct **68a** in quantitative yield and moderate enantioselectivity (39% ee) (Table 8). Then, after examining various Michael acceptors and donors, which afforded unsatisfactory results, the enantioselective Michael addition of different β-keto esters **67a**–**e** to methyl vinyl ketone and acrolein, catalyzed by the (*R*)-**2**-$Sc(OTf)_3$ complex, was investigated. As shown in Table 8, the bulkiness of the ester substituent had a pronounced effect on the observed enantioselectivity, which increases with the bulkiness of the ester. The stereochemical result may be explained by the transition model **69**. The bulky *tert*-butyl ester moiety should be located on the *si*-face of the keto ester plane in order to avoid the steric repulsion with the quinoline moiety, which leads the attack of the methyl vinyl ketone (MVK) at the *re*-face preferentially.

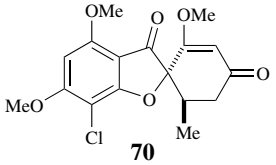
Table 8. Enantioselective Michael addition of β-keto esters **67a**–**e** to methyl vinyl ketone or acrolein catalyzed by the (*R*)-**2**-$Sc(OTf)_3$ complex (Scheme 17)[25]

Donor	R	Acceptor	Adduct	Yield (%)	Ee (%)
67a	Me	CH_2=CHCOMe	**68a**	98	39
67b	$PhCH_2$	CH_2=CHCOMe	**68b**	85	38
67c	*i*-Pr	CH_2=CHCOMe	**68c**	94	47
67d	$(i\text{-Pr})_2CH$	CH_2=CHCOMe	**68d**	98	69
67e	*t*-Bu	CH_2=CHCOMe	**68e**	89	84
67e	*t*-Bu	CH_2=CHCHO	**68e**	73	75



69

Next, this type of Michael addition was applied to the enantioselective synthesis of the biologically active compound griseofulvin **70**.

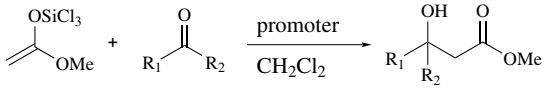


70

As a model for synthesizing **70**, the Michael addition of *tert*-butyl 3-oxobenzo[*b*]furan-2-carboxylate **71**, an oxygen analogue of **67e** was investigated (Scheme 18). The reaction of **21** with methyl vinyl ketone proceeded smoothly to afford **72a** in 77% ee. Although the diastereoselectivity was modest (2:1), the reaction of 3-penten-2-one also proceeded smoothly to give 76% enantiomeric excess. Following these findings, the Michael addition of *tert*-butyl 3-oxofurancarboxylate **74** was studied (Scheme 19). Unfortunately, neither diastereoselectivity nor enantioselectivity were observed. This dramatic reduction of selectivity was attributed to the steric repulsion between a methoxy group of the substrate and the quinoline ring of **2**.

2.5. Aldol addition to ketones

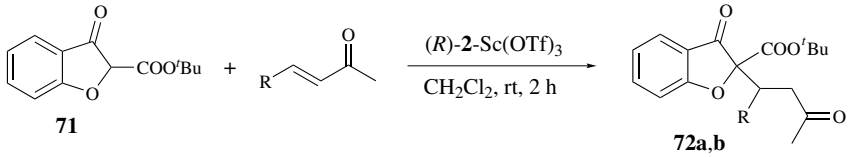
Denmark and Fan have recently undertaken the first steps towards the realization of catalytic enantioselective aldol additions[26] of ester trichlorosilyl enolates to ketones[27] (Scheme 20). A number of promoters (Me_3NO, NMO, quinuclidine *N*-oxide and pyridine *N*-oxide) at different temperatures (−20 to −78 °C), were assessed for the addition of trichlorosilyl ketene acetal **76** to acetophenone (Scheme 20, $R_1 = Ph$, $R_2 = Me$). It was found that pyridine *N*-oxide possessed the greatest capability to promote the aldol reaction. Then, a series of ketones with representatives in all basic structural classes (16 examples: aromatic, heteroaromatic, olefinic, acetylenic, aliphatic, branched and linear) were submitted to the addition of **76** in the presence of pyridine *N*-oxide as the catalyst (10 mol%). All reactions proceeded cleanly affording high yields of the corresponding addition products **78**. Only pinacolone and 2-tetralone afforded unsatisfactory outcomes.



76 **77** **78**

Scheme 20.

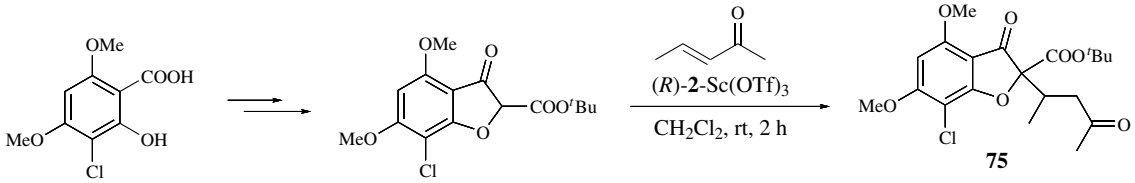
Having found an efficient catalytic system, the search for a suitable chiral catalyst was initiated. Initial studies with camphor-derived pyridine *N*-oxides were disappointing, both in terms of reactivity and selectivity. On considering that in the process two molecules of the catalyst are involved in the stereochemistry-determining transition structure, chiral C_2-symmetric *N*,*N*′-dioxides were employed. These ligands were the 2,2′-biquinoline (*S*)-**2**, the 1,1′-biisoquinoline (*R*)-**4** and the 2,2′-bipyridines **79a**,**b** and **80a**–**c** (Scheme 21).



71 **72a**,**b**

72a: (R = H, 89%, 77% ee)
73b: (R = Me, 86%,* 76% ee (major), 9% ee (minor))
*mixture of diastereomers (2:1)

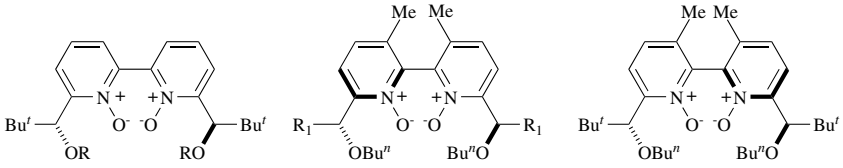
Scheme 18.



73 **74** **75**

81%,* <10% ee for both diasrereomers
*mixture of diastereomers (1:1)

Scheme 19.



(*R*,*R*)-**79a**: R = Me (*aS*,*R*,*R*)-**80a**: R_1 = *t*-Bu (*aR*,*R*,*R*)-**80c**
(*R*,*R*)-**79b**: R = *n*-Bu (*aS*,*R*,*R*)-**80b**: R_1 = $PhMe_2C$

Scheme 21.

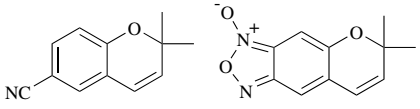
Ligands **79a**,**b** were prepared by MCPBA oxidation of the parent bipyridines, which were easily accessible by repeating the Bolm et al. procedures.[28] Ligands **80a**–**c**, in which the 3,3′-methyl groups serve to fix the configuration of the chiral axis, were prepared following the same protocol used for the synthesis of **79a**,**b**.

The *N*,*N*′-dioxides (*S*)-**2** and (*R*)-**4** catalyzed the addition of **76** to acetophenone, but with modest enantioselectivity (26–45% ee). The use of *N*,*N*′-dioxides **79a**,**b** improved the enantioselectivity up to 64% ee. Further increase was achieved employing the atropisomeric *N*,*N*′-dioxides **80a**,**b**. Thus, when the reaction was carried out at −20 °C for 12 h, (*aS*)-**80a** and (*aS*)-**80b** afforded the methyl ester of 3-hydroxy-3-phenylbutanoic acid in 84% and 80% ee, respectively, The ligand (*aR*-**80c** catalyzed the same aldol addition in high yield, but afforded the opposite enantiomer with modest enantioselectivity (43% ee). Aldol reaction of the 16 ketones used previously was then examined using (*aS*)-**80a** as the catalyst. In general, aromatic ketones gave the higher enantioselectivities (80–86% ee). Olefinic ketones were the poorer performers (8–11% ee), inferior even to aliphatic ketones (20–41% ee).

2.6. Epoxidation of olefins

Miura and Katsuki studied the asymmetric epoxidation of olefins using achiral (Salem)manganese(III) complexes in combination with an *N*,*N*′-dioxide as a chiral ligand.[29] These chiral ligand binds to the manganese complex in the axial position affecting its conformation and so making the new complex chiral. In particular, the epoxidation of 6-acetamido-2,2-dimethyl-7-nitrochromene **81** using the manganese complexes **83a** and **83b** as catalysts and the axially chiral bipyridine *N*,*N*′-dioxides **2** and **84** as donor ligands was examined (Scheme 22).

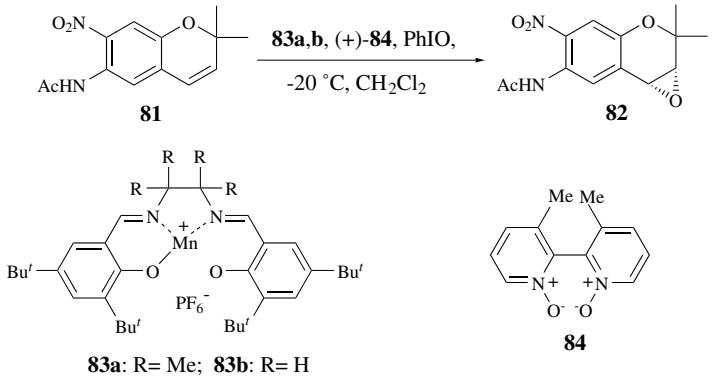
The epoxidation of **81** using both **83a** and **83b** in the presence of the known *N*,*N*′-dioxide **2** afforded the epoxide **82** in low yield and enantioselectivity. To increase the coordination constant probably at the expense of the interaction between the axial ligand and the salen ligand, 3,3′-dimethyl-2,2′-bipyridine *N*,*N*′-dioxide **84** was synthesized, which is smaller than **2**. The racemic *N*,*N*′-dioxide **84** was prepared by MCPBA oxidation of the parent bipyridine and resolved successfully via a hydrogen-bonded complex with (*S*)- or (*R*)-binaphthol. Although, the combination of the complex **83a** with **84** afforded disappointing results in the epoxidation of **1**, the substitution of **83a** by **83b** resulted in high enantioselectivity (82% ee) and good chemical yield (62%). Two other chromene derivatives **85** and **86** were submitted to asymmetric epoxidation. Yields and enantioselectivities were similar to that obtained with **1** (59% and 77% ee for **6**; 60% and 78% ee for **7**).



85 **86**

2.7. Desymmetrization of *meso*-epoxides

Fu and Nakajima described the use of chiral pyridine *N*-oxides in the catalytic enantioselective desymmetrization



81 **82**

83a: R= Me; **83b**: R= H **84**

Scheme 22.

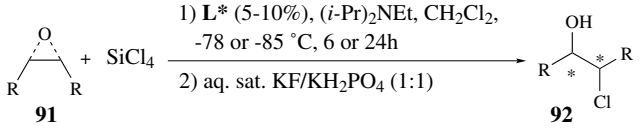
of *meso*-epoxides; the latter is an attractive strategy for asymmetric synthesis since it simultaneously establishes two contiguous stereogenic centres.[30]

Fu et al. achieved the catalytic enantioselective desymmetrization of *meso*-epoxides with chlorosilanes[31] and chiral pyridine *N*-oxides **3a**–**c**.[32] The parent pyridines of these oxides were easily accessible by one-pot treatment of $FeCl_2$ with C_5R_5Li (**87a**–**c**), followed by the pyridinyl anion **90** (Scheme 23). Oxidation with dimethyldioxirane of ferrocenes **88a**–**c** then furnished the racemic pyridine *N*-oxides **89a**–**c**, which were readily resolved by chiral HPLC. The absolute configuration of (−)-**89b** was determined by X-ray crystallography.

The pyridine *N*-oxides **89a**–**c** efficiently catalyzed the ring-opening of *cis*-stilbene oxide with $SiCl_4$ to give 2-chloro-1,2-diphenylethanol (Scheme 24). The enantioselectivity was found to depend on the steric demand of the substituents on the cyclopentadienyl group (**89a** and **89b** gave 11% and 25% ee, respectively, at room temperature; **89b**, 60% ee at −78 °C; **89c**, 68% ee at room temperature and 92% ee at −78 °C). Under optimized conditions [**89c** (5 mmol %), $(i\text{-Pr})_2NEt$, CH_2Cl_2, −85 °C, 24 h] a number of epoxides were desymmetrized in very good yield and high stereoselection to give the corresponding chlorohydrins with (*S*,*S*)-configuration (Scheme 24: R = Ph (88%, 94% ee); R = 4-FC_6H_4 (97%, 91% ee); R = 4-$CH_3C_6H_4$ (94%, 93% ee); R = 4-$CF_3C_6H_4$ (93%, 98% ee); R = 2-naphthyl (84%, 94% ee); R = CH_2OBn (91%, 50% ee)).

Nakajima et al. examined the same reaction, exploiting chiral bipyridine *N*,*N*′-dioxides as chiral catalysts.[33] The addition of $SiCl_4$ to *cis*-stilbene oxide using (*S*)-**2** (10 mol %) as the catalyst $(i\text{-Pr})_2NEt$, CH_2Cl_2, −78 °C, 6 h) was initially examined. The reaction afforded the corresponding chlorohydrin in 94% yield, but the enantioselectivity (56% ee) was moderate. Satisfactory results were found employing (*S*)-**4** as the catalyst (95%, 90% ee). Ring opening of other epoxides was also examined. Epoxides derived from 2-butene-1,4-diols [Scheme 24: R = CH_2OCH_2Ph and $CH_2O(CH_2)_3Ph$] afforded the corresponding chlorohydrins in good enantioselectivity and with (*S*,*S*)-configuration (98% and 95% yield, 74% and 70% ee, respectively), while cyclohexene oxide gave racemic product (83% yield).

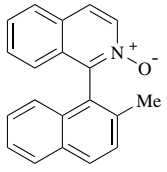
Fu found a positive nonlinear correlation between the ee of the catalyst and the ee of the chlorohydrin in the



91 **92**

Scheme 24.

opening reaction catalyzed by their planar-chiral pyridine oxide **89**. Since this observation suggested the possibility of coordination of a second *N*-oxide molecule to silicon to form a hexacoordinate silicate, Nakajima assumed that ligands (*S*)-**2** and (*S*)-**4** could act as bidentate ligands to form hexacoordinate silicate intermediates during the catalytic cycle of the reaction. To test this hypothesis, epoxide opening using the monodentate *N*-oxides **93** and **58** (see Scheme 13) was examined. These ligands were prepared by palladium-catalyzed coupling of 2-chloroisoquinoline and 2-methyl- or 2-methoxy-1-naphthylborate, followed by oxidation with MCPBA. Resolution was finally obtained through the hydrogen bonding complex with (*R*)- or (*S*)-binaphthol, respectively. A significant decrease of the catalytic activity and enantioselectivity was observed with both ligands. These data were explained by invoking the formation of hexacoordinate silicate intermediates, though the details were not clear.

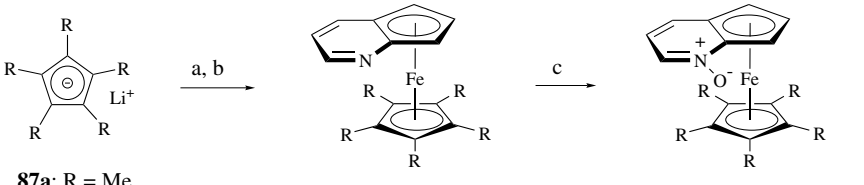


(-)-**93**

Kocovsky et al. has also anticipated that the ligand (+)-**18** (Scheme 6) is able to promote the cleavage cyclooctene epoxide with $SiCl_4$ to afford the corresponding chlorohydrin of 85% ee, which is the highest enantioselectivity reported to date.[13]

2.8. Cyanation of imines

Feng et al. exploited chiral pyridine *N*,*N*′-dioxides as promoters in the asymmetric cyanation of imines[34,35] (Scheme 25), that with the classic Strecker reaction is one of the most important reactions for the production



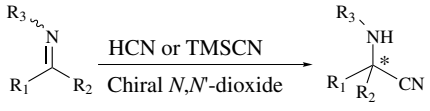
87a: R = Me
87b: R = Ph
87c: R = 3,5-$Me_2C_6H_3$

88a: R = Me, 50%
88b: R = Ph, 52%
88c: R = 3,5-$Me_2C_6H_3$, 67%

89a: R = Me, 79%
89b: R = Ph, 45%
89c: R = 3,5-$Me_2C_6H_3$, 92%

Scheme 23. Reagents and conditions: (a) $FeCl_2$; (b) **90**; (c) dimethyldioxirane

90



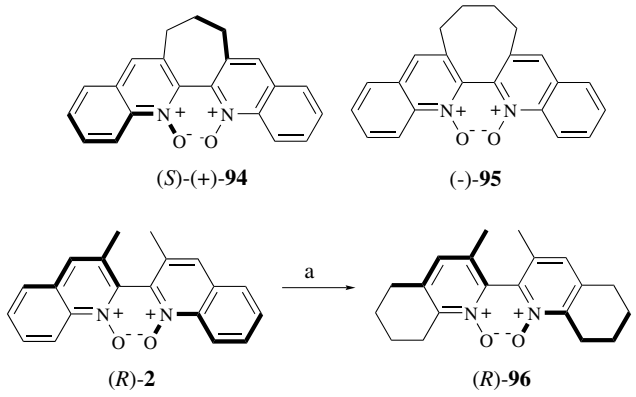
Scheme 25.

of α-amino nitriles,[36] the latter being key intermediate for the synthesis of α-amino acids.

The series of axially chiral *N*,*N*′-dioxides (*R*)-**2**, (*R*)-**4**, (*S*)-**94**, (−)-**95** and (*R*)-**96** were assessed in the enantioselective addition of HCN or trimethylsilylcyanide (TMSCN) to aryl aldimines ($ArCH{=}NCHPh_2$).[34,35] The racemic *N*,*N*′-dioxides **94** and **95** were prepared according to a procedure described by Thummel and Lefoulon[37] and resolved with L- or D-dibenzoyltartaric acid, respectively. Compound (*R*)-**96** was prepared by hydrogenation of (*R*)-**2** in the presence of PtO_2 in CF_3COOH (94% yield) (Scheme 26).

The reaction of benzaldehyde *N*-benzhydrylimine (0.05 M in CH_2Cl_2, −25 °C, 24 h) with HCN (ratio imine/HCN = 1:1) in the presence of C_2-symmetric *N*,*N*′-dioxides (1 equiv), gave the amino nitrile in poor yield (0–31%) and in low to moderate enantiomeric excess (13–62%). The ligand (*R*)-**2** was the best promoter among the screened *N*,*N*′-dioxides (62% ee).

It was next found that in the presence of (*R*)-**2**, TMSCN could act as another effective cyanating agent. Thus, the reaction of benzaldehyde *N*-benzhydrylimine **97** using TMSCN at 0 °C instead of HCN, afforded the product in better yield, but the enantioselectivity never exceeded 66% ee, although many permutations of reaction conditions were carried out (solvent, temperature, amount of the promoter and concentration of the substrate).

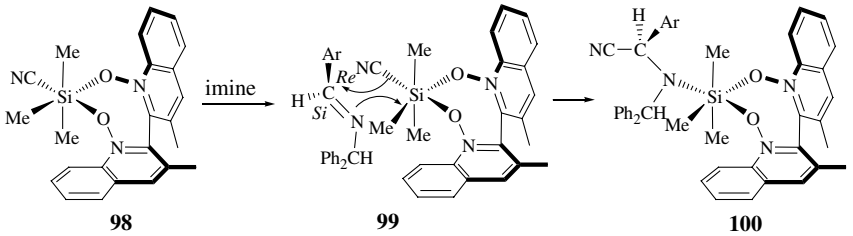


Scheme 26. Reagents and conditions: (a) H_2, PtO_2, CF_3COOH, rt, 94%.

Under the optimal conditions [(*R*)-**2**: 1 equiv, imine: 0.2 M in CH_2Cl_2, 0 °C, ratio imine/TMSCN = 1:1.5 or 1:2] a number of aromatic, heteroaromatic and conjugated aldimines ($ArCH{=}NCHPh_2$) afforded the corresponding α-amino nitriles with moderate to excellent enantioselectivities and yields (representative examples: Ar = Ph, 67%, 67% ee; Ar = 2-ClC_6H_4, 96%, 95% ee; Ar = 3-$O_2NC_6H_4$, 87%, 88% ee; Ar = 4-ClC_6H_4, 93%, 78% ee; Ar = 2-furyl, 86%, 49% ee; Ar = PhCH=CH, 88%, 67% ee). In some cases, enantiomerically pure products (99% ee) were obtained by simple recrystallization.

Some experiments were carried out to elucidate the significant 'nucleophilic effect' of the *N*-oxides at silicon and their potential role in the reaction. Compounds *rac*-**2**, *rac*-3,3′-dimethyl-2,2′-biquinoline *N*-monoxide and 3,3′-dimethyl-2,2′-biquinoline were chosen to investigate the promotion of the Strecker reaction between benzaldehyde *N*-benzhydrylimine and TMSCN. Under the general reaction conditions, these ligands afforded the product with 88%, 76% and 60% yields, respectively, indicating that the strong donor (N–O) could play the most important role in enhancing reactivity and nucleophilicity of TMSCN, whereas the weak donor (N) could have only a small effect on the silicon atom. On the basis of these data and those obtained by the ^1H and ^{29}Si NMR spectra recorded under several systems (TMSCN, TMSCN + *rac*-**2**, TMSCN + *rac*-N-monoxide and TMSCN + *rac*-**2** + imine), it was possible to propose reaction transition states to account for the observed asymmetric induction of (*S*)-**2** (Scheme 27).

The mechanistic hypothesis suggests that when TMSCN is added to the solution of (*S*)-**2**, the strong electron donors (N–O) of (*S*)-**2** coordinate to the silicon atom of TMSCN to form the hexacoordinate hypervalent silicate **98**, so the nucleophilicity of the cyano group of **98** is enhanced. The highly reactive cyano group then attacks the imine from the *re*-face and the nitrogen atom simultaneously coordinates to the silicon atom to produce another hexacoordinate hypervalent silicate **100**, which ultimately forms the desired Strecker adduct with (*R*) configuration.



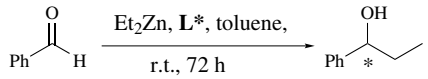
Scheme 27.

2.9. Reduction of ketones and addition of diethylzinc to benzaldehyde

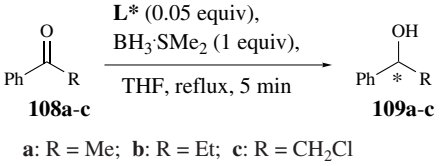
Laschat et al. used chiral pyridine *N*-oxides in the enantioselective catalytic reduction of ketones and addition of diethylzinc to benzaldehyde.[38] C_1- and C_2-symmetric ligands **103a–e** and **106a–e**, respectively, were prepared starting from picolinic acids **101** and **104** (Scheme 28). Oxidation of these acids with hydrogen peroxide in AcOH gave the corresponding *N*-oxides **102** and **105** in good yields (76–79%). The condensation of these *N*-oxides with L-amino acid esters or (1*R*,2*S*)-norephedrine, carried out employing bromotrichloromethane/triphenylphosphine for the activation of the carboxylic acids,[39] gave the desired chiral amides in moderate yields (30–59%). For a comparison, the 2,6-bis(aminoacyl)pyridines **107d** and **107e** were prepared by converting **104** into the 2,6-diacyl chloride, which was next treated with methionine methyl ester or norephedrine, respectively (Scheme 28).

Compounds **103**, **106** and **107** were used as chiral ligands in two catalytic asymmetric transformations. In the catalytic addition of diethylzinc to benzaldehyde to give 1-phenylpropan-1-ol (Scheme 29),[40] low enantioselectivities (2–29% ee) were obtained with ligands **103** and **106**, regardless of the amino acid moiety. By contrast, the corresponding 2,6-bis(aminoacyl)pyridines **107d** and **107e** led to increased ee values (55% ee).

In the catalytic reduction of ketones **108a–c** to alcohols **109a–c** with $BH_3{\cdot}SMe_2$ (Scheme 30),[41] low enantioselectivities were observed for the alanine-, valine- and leucine-derived *N*-oxides **103a–c** and **106b,c**. An increase of selectivity was obtained with the bis-methionine ligand **106d** (32–38% ee) relative to that of monomethionine ligand **103d** (7–16% ee). However, mononorephedrine ligand **103e** (⩽64% ee) and the corresponding C_2-symmetric **106e** (⩽51% ee) displayed the highest enantioselectivities. The influence of the *N*-oxide moiety on the enantioselecivity was demonstrated by the observation that 2,6-bis(aminoacyl)pyridines **107d** and **107e** gave much lower selectivities (⩽14% ee) than the corresponding pyridine *N*-oxides **106d** and **106e**.



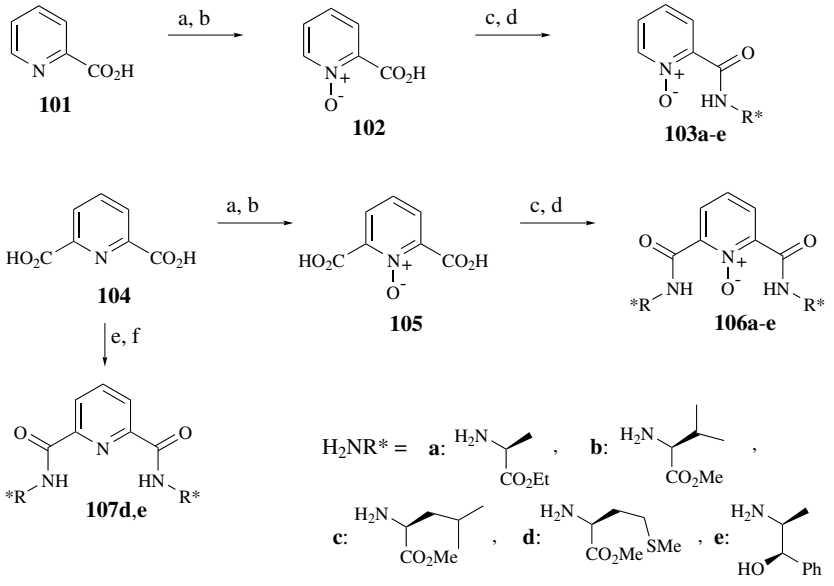
Scheme 29.



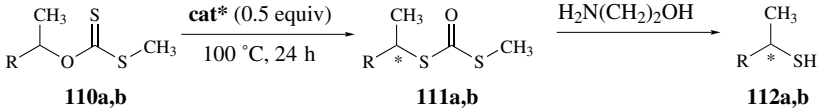
Scheme 30.

2.10. Synthesis of thiols by thione–thiol rearrangement

Marchetti et al. studied the enantioselective synthesis of thiols by thione–thiol rearrangement catalyzed by optically active pyridine *N*-oxides (Scheme 31).[42] The racemic thiones **110a** and **110b** as starting materials and the chiral pyridine *N*-oxides **113**, **114** and **115a,b** as catalysts were used (Scheme 32). These pyridine derivatives were prepared by oxidation of the corresponding known chiral pyridines with MCPBA. In the oxidation of nicotine, the two diastereomeric *N*-oxides **115a** and **115b**



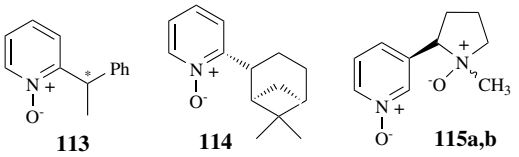
Scheme 28. Reagents and conditions: (a) KOH, MeOH; (b) AcOH, H_2O_2, 80 °C, 27 h; (c) $BrCCl_3$, PPh_3; (d) H_2NR^*, THF, reflux, 16 h; (e) $SOCl_2$, reflux, 2 h; (f) H_2NR^*, rt, 3 h.



110a,b **111a,b** **112a,b**

a: R = Et; **b**: R = Ph

Scheme 31.



113 **114** **115a,b**

Scheme 32.

were obtained in a 0.8:1 ratio. This mixture was not separated, but was used as such.

The reactions were carried out at 100 °C for 24 h, using 50 mol% of the catalyst. The rearrangement products were obtained in moderate to good yields (49–80%), but the reactions were not stereoselective with ligands **113**, **114** and afforded low enantiomeric excesses with ligands **115a**,**b** (38% and 11% ee for the substrates **110a** and **110b**, respectively).

The proposed mechanism for the thione–thiol rearrangement (Scheme 33) shows that there are three steps, which could influence the enantioselectivity: (a) formation of **116**, (b) rearrangement–fragmentation and (c) transformation of **117** into the product. The authors did not determine which step plays the major role.

3. Conclusion

This review reports the syntheses and applications of chiral pyridine *N*-oxides as chiral controllers for asymmetric reactions. The potential of chiral pyridine *N*-oxides has been demonstrated in several catalytic processes, however, their versatility as chiral controllers in asymmetric catalysis still remains to be developed. In fact, the availability of these chiral ligands is still limited, because their preparation has only recently been undertaken. It is tempting to predict that many processes involving a high degree of stereocontrol will become available as an increasing number of derived of chiral pyridine *N*-oxides become available.

Acknowledgements

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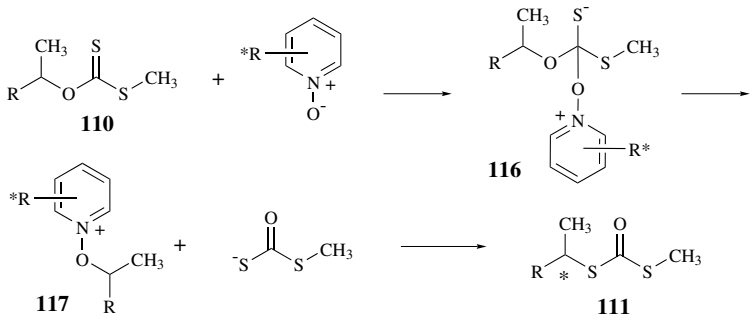

110 **116** **117** **111**

Scheme 33.

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