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Pyridine *N*-Oxides and Derivatives Thereof in Organocatalysis

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Abstract Pyridine *N*-oxides are a class of mild Lewis bases that can activate certain kinds of Lewis acidic parts of molecules and hence increase reactivity of its nucleophilic part towards various reactions with electrophiles. This review aims to summarize the applications of various non-chiral and chiral pyridine *N*-oxides in catalysis of a variety of reactions. In addition, the applications of these reactions in syntheses of natural and bioactive compounds are mentioned as well.

Keywords Aldol reactions • Allylation • Catalysis • Crotylation • Cyanation • Epoxide • Epoxide cleavage • Natural compounds • *N*-oxide • Phosphorylation • Propargylation • Rearrangement • Reduction • Synthesis

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1 Introduction

Compounds possessing one, two, or more pyridine *N*-oxide moieties as the part of their molecular framework constitute a special class of compounds with unique properties. Probably the most frequent use of such compounds is in various oxidation reactions where they act as oxidants. However, this review aims to focus on the use of pyridine *N*-oxides as mild Lewis bases that can activate Lewis acid parts of molecules and hence increase reactivity of its nucleophilic part towards various reactions with electrophiles. Although catalytic activity of compounds possessing the pyridine *N*-oxide moiety has been partially reviewed or mentioned several times in different reports during the past two decades [1–13], the goal of this review is to gather a more comprehensive set of information on catalytic activity and applications of pyridine *N*-oxides in promotion of various racemic and enantioselective reactions.

First of all, it should be noted that pyridine *N*-oxides can be found in nature. Usually these compounds are highly toxic. As a typical example may serve orellanine **A** – a mycotoxin – isolated from the Fool's webcap (*Cortinarius orellanus*) (Fig. 1) [14, 15]. It is a highly poisonous substance with nephrotoxic properties. Poisoning results in renal failure and irreversible damage of kidneys. Other pyridine *N*-oxides possessing antibacterial activity such as 2-(methyldithio)pyridine-*N*-oxide **B**, 2-[(methylthiomethyl) dithio]pyridine-*N*-oxide **C**, and 2,2′-dithio-bis(pyridine-*N*-oxide) **D** were isolated from Persian shallot (*Allium stipitatum*) [16].

N-oxides are also found in the realm of pharmaceutically active substances (Fig. 2). As typical examples may serve SCH 350634 **E** and SCH 341125 **F** that serve as selective CCR5 receptor antagonists with potent anti-HIV activity [17], a potent thrombin inhibitor **G** [18, 19], and JPL-32 **H** a representative of *N*-oxides with anti-HIV properties with multiple mechanisms of antiviral action [20].

2 Physical Properties of Pyridine *N*-Oxides

Pyridine *N*-oxides are Lewis bases, because the N–O moiety of pyridine *N*-oxides, thanks to high polarization, might act as an electron donor. Hence they may combine with Lewis acids forming the corresponding Lewis acid–base pairs. This property has an essential chemical consequence, because it can increase the nucleophilicity of the Lewis acids towards potential electrophiles and thus allow them to react under conditions under which they otherwise would not react.

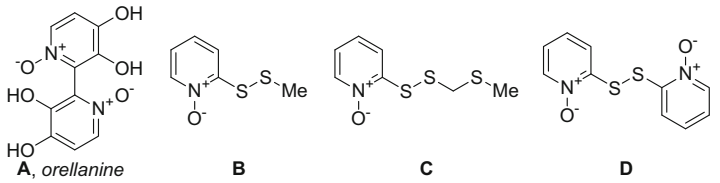


Fig. 1 Orellanine and other natural compounds possessing the *N*-oxide moiety

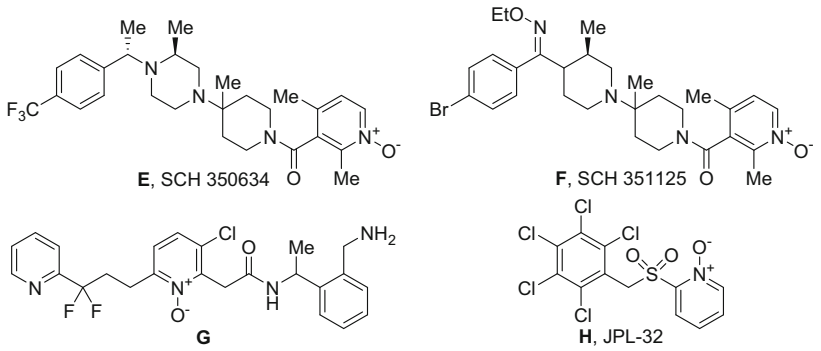


Fig. 2 Pharmaceutically active substances possessing the *N*-oxide moiety

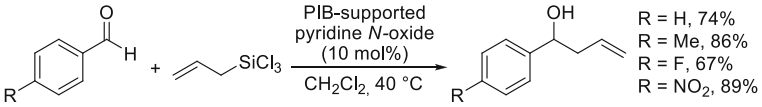
Although the basicity of the pyridine *N*-oxides is lower in comparison with the corresponding pyridines, it is often sufficient enough to activate a number of various Lewis acids and thus catalyze a number of various reactions. Basicity of pyridine *N*-oxides and their respective reactivity towards numerous Brønsted and Lewis acids has been studied in a number of cases and for their pK_a and other data see elsewhere [21–26].

3 Non-chiral Pyridine *N*-Oxide Catalyzed Reactions

Only a handful of reactions catalyzed by non-chiral *N*-oxides have been reported. Among them belong allylation of aldehydes, aldol reaction, Passerini-type reaction, and phosphorylation of alcohols.

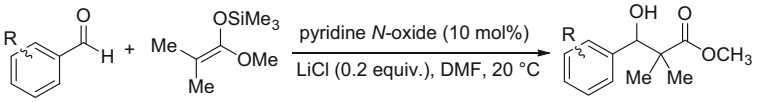
Polyisobutylene-supported pyridine *N*-oxide was shown to catalyze allylation of several aromatic aldehydes with allyltrichlorosilane (Scheme 1) [27]. These studies demonstrated that it is a highly active and recyclable catalyst that promotes the allylation of aromatic aldehydes in yields up to 99%. It could be successfully recycled up to five times by extraction with a mixture of hexane/90% EtOH–H_2O. The recycled catalyst retained its catalytic efficiency.

Pyridine *N*-oxide and DMAP *N*-oxide were used to catalyze aldol reaction of trimethylsilyl dimethylketene acetal with various aromatic (Table 1) and other aldehydes



Scheme 1 Allylation of aldehydes catalyzed by a polymer supported pyridine *N*-oxide

Table 1 Aldol reactions with substituted benzaldehydes



R	Time (h)	Yield (%)[a]
H	5	83
4-NO_2	23	87
2-Cl	12	65
4-Cl	10	77
4-MeO	10	44
4-HO	21	96
4-AcO	15	80
4-*t*-$BuMe_2SiO$	10	62
4-MeS	21	87

[a]Isolated yields

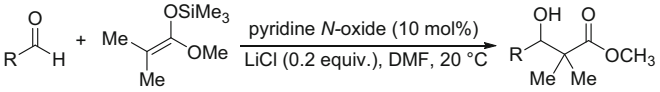
(Table 2) [28]. The reaction was carried out in DMF and in almost all cases it proceeded to furnish aldol products in high yields.

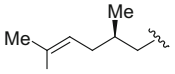
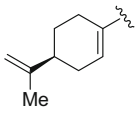
The Passerini reaction is based on the reaction of a mixture of an isocyanide with a ketone or an aldehyde in the presence of a carboxylic acid to give an α-acyloxy carboxamide. Pyridine *N*-oxide was shown to catalyze the reaction of $SiCl_4$ with benzaldehyde and *tert*-butyl isocyanide to the corresponding α-hydroxy amide after basic hydrolysis in 94% yield (Scheme 2) [29].

Recently, it has been shown that various 2-aryl-4-(dimethylamino)pyridine-*N*-oxides can serve as efficient phosphorylation catalysts for amino acids and polyols (Scheme 3) [30]. The most effective catalyst was 2-(2,4-bistrifluoromethylphenyl)-4-dimethylaminopyridine *N*-oxide. Synthetic usefulness of this procedure was also demonstrated by a selective phosphorylation of the tyrosine hydroxyl group in a heptapeptide.

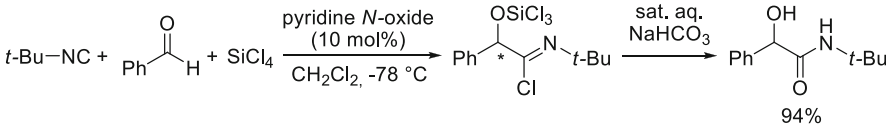
As far as other reactions catalyzed by pyridine *N*-oxides are concerned, it is worth to mention: (1) a positive catalytic effect of 4-substituted pyridine *N*-oxides on silylation of alcohols [31, 32], (2) effect of pyridoxal *N*-oxide on racemization of amino acids [33], 4-substituted pyridine *N*-oxides for catalysis of hydrolysis of 2,3,5,6-*p*-benzoquinone [34], the use of pyridine *N*-oxide as a cocatalyst for arylsulfonylation and benzoylation of phenols [35, 36], and finally the use of 4-dimethylamino pyridine *N*-oxide as an efficient catalyst in peptide synthesis [37].

Table 2 Aldol reactions with other aldehydes

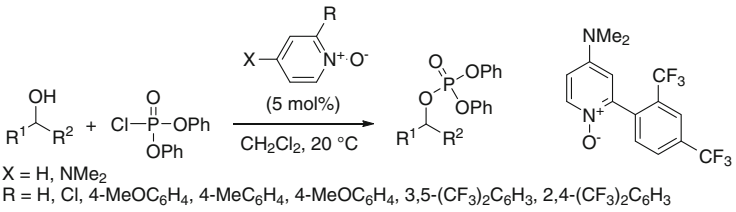


R	Time (h)	Yield (%)[a]
6-Methylpyrid-2-yl	5.5	55
$PhCH_2CH_2$	5	80
	5	81
$Me(CH_2)_8$	7	78
4-*t*-$BuMe_2SiO$	10	62
	10	91

[a]Isolated yields



Scheme 2 Passerini-type reaction catalyzed by pyridine *N*-oxide



Scheme 3 Phosphorylation of alcohols catalyzed by a substituted pyridine *N*-oxide

4 Reactions Catalyzed by Chiral Pyridine *N*-Oxides and Their Derivatives

4.1 Synthesis of Chiral Pyridine N-*Oxides,* N,N′-*Dioxides, and Related Compounds*

Compounds possessing the pyridine *N*-oxide moiety could be divided into several classes with respect to their elements of chirality within their scaffold and can be

classified into the following groups: (a) those possessing the element of axial chirality (Fig. 3), (b) those possessing the element of central chirality (Figs. 4–6), (c) those possessing the element of planar chirality (Fig. 7), (d) those possessing the element of helical chirality (Fig. 8), and, finally, (e) those possessing several elements of chirality (axial and central) (Fig. 9).

At the outset, the pyridine *N*-oxides possessing the element of axial chirality are dealt with. Historically the first chiral bipyridine *N*,*N*′-dioxide **1a** was prepared and resolved into enantiomers by Fujii et al. [38, 39] but it was Nakajima et al. [40] who

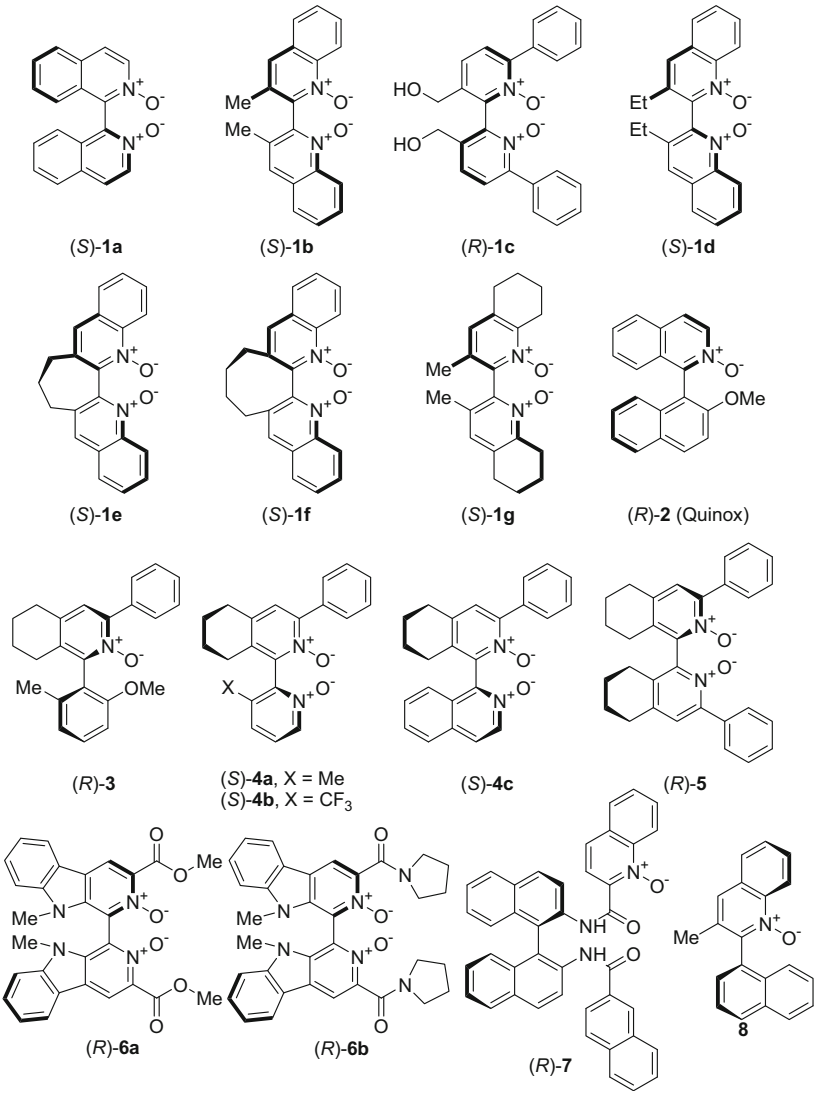


Fig. 3 Various pyridine *N*-oxides possessing elements of axial chirality

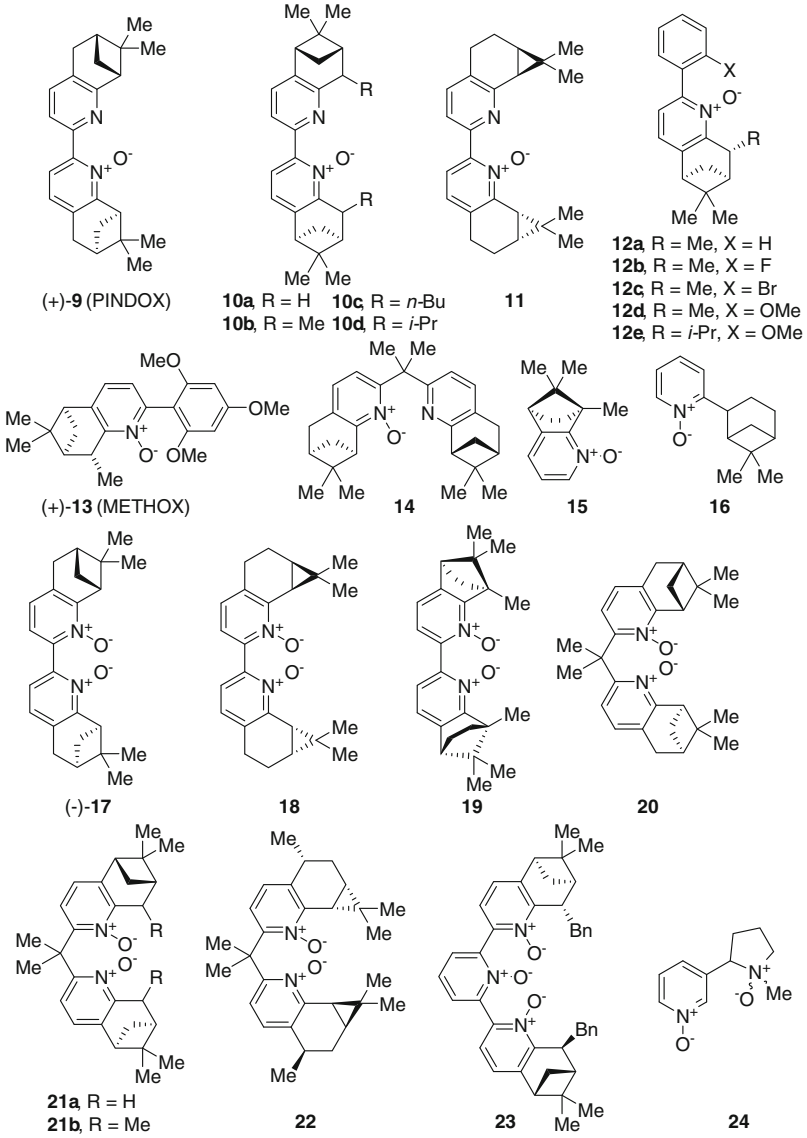


Fig. 4 Various pyridine *N*-oxides possessing elements of central chirality derived from terpenes and alkaloids

reported the first use of **1a** and its analog **1b** (Fig. 3) in organocatalysis. These achievements provided the necessary impetus that prompted others to join, expand, and develop the area of organocatalytic allylations into a matured field. The compound **1c** with a similar framework was prepared by Hayashi et al. [41, 42]. Other analogs such as **1d**, prepared by Chang et al. [43], and **1e–1g**, prepared by Feng et al. [44],

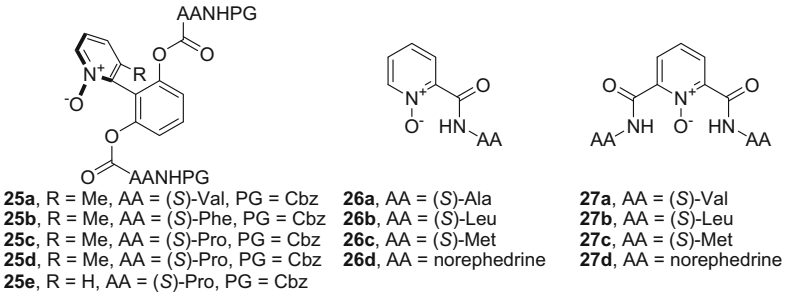


Fig. 5 Various pyridine *N*-oxides possessing elements of central chirality derived from amino acids

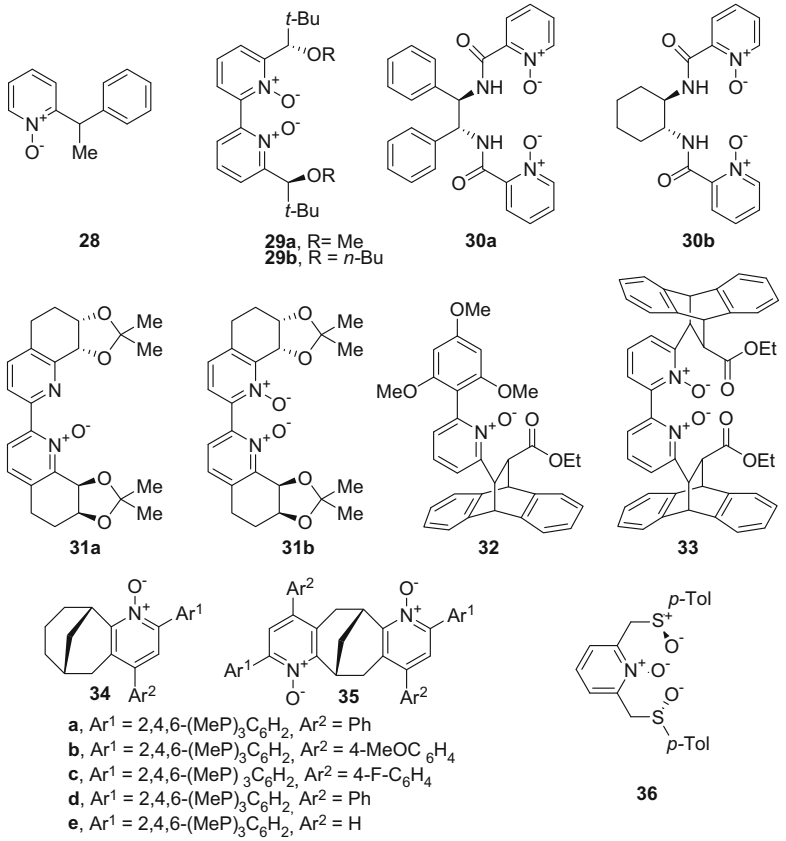


Fig. 6 Various pyridine *N*-oxides possessing elements of central chirality

were reported. Among these compounds axially chiral *N*-oxides **2** prepared by Kočovský et al. [45] and **3** prepared by Kotora et al. [46] could be also included.

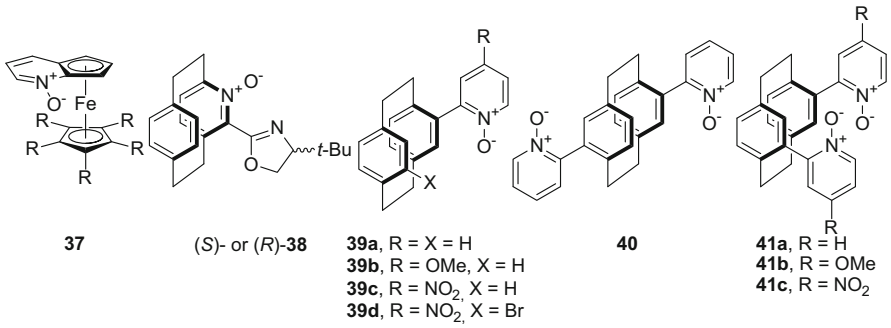


Fig. 7 Various pyridine *N*-oxides possessing elements of planar chirality

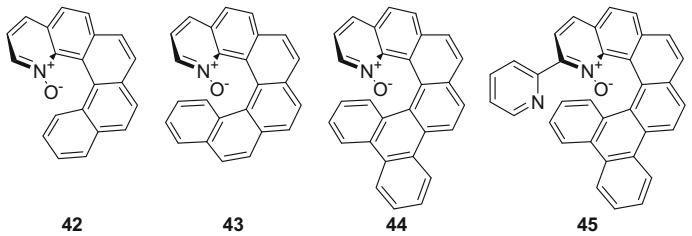


Fig. 8 Various pyridine *N*-oxides possessing elements of helical chirality

Further generations of unsymmetrically and symmetrically substituted chiral bipyridine *N*,*N*′-dioxides comprise **4a–4c**, and **5** possessing the tetrahydroisoquinoline framework, prepared by Kotora et al. [47–50], and, finally, *N*,*N*′-dioxides bearing the carbazole framework **6a** and **6b** prepared by Zhu et al. [51, 52]. Also a pyridine *N*-oxide with a chiral biphenyl moiety **7** prepared by Benaglia et al. [53] should be mentioned as well. A new type of catalyst **8** possessing the element of axial chirality was reported by Nakajima et al. [54] and a related compound also by Yu et al. [55].

Regarding the synthesis of bipyridine *N*-oxides and *N*,*N*′-dioxides possessing elements of central chirality, numerous compounds possessing different molecular scaffolds have been prepared (Figs. 4–6). Among them belong *N*-oxides derived from chiral natural terpenes (Fig. 4) such as bipyridine mono-*N*-oxides **9** [56], **10** (*iso*-PINDOX series) and **11** [57], structurally related pyridine *N*-oxides **12** [58] and **13** [59] prepared by Kočovský et al., **14** prepared by Benaglia et al. [60], **15** prepared by Denmark et al. [61], and, finally, **16** prepared by Marchetti et al. (absolute configuration was not given) [62]. Representatives of *N*,*N*′-dioxides are bipyridine *N*,*N*′-dioxide **17** and **18** prepared by Kočovský et al. [56, 57], bipyridine *N*,*N*′-dioxide **19** prepared by Denmark et al. [61], and bridged bipyridine *N*,*N*′-dioxides **20–22** prepared by Benaglia et al. [60]. Finally, *N*,*N*′,*N*″-trioxide **23** was prepared by Kwong et al. [63]. Among other *N*-oxides originating from natural source belongs a diastereomeric mixture of (1′*R*,2′*S*)- and (1′*S*, 2′*S*)-3-(1-methyl-2-pyrrolidinyl)pyridine *N*,*N*′-dioxides **24** synthesized by oxidation of (*S*)-(−)-3-(1-methyl-2-pyrrolidinyl)pyridine (nicotine) by Marchetti et al. [61].

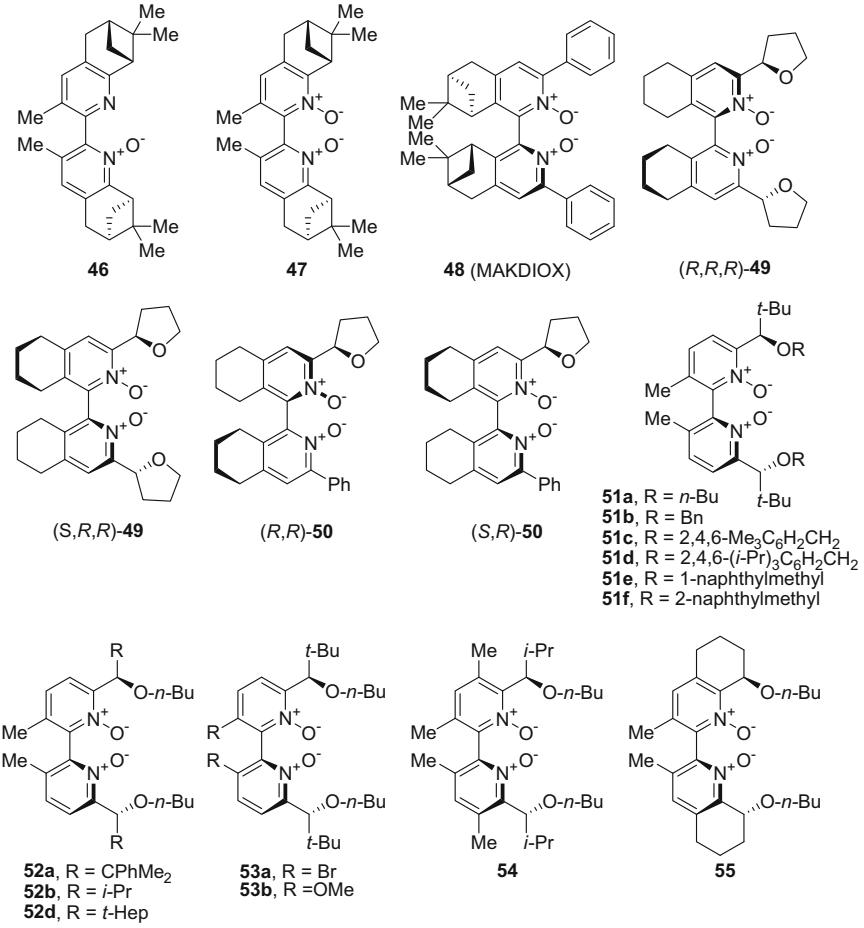


Fig. 9 Various pyridine *N*-oxides possessing elements of axial and central chirality

Another class of pyridine *N*-oxides possessing central chirality is derived from amino acids (Fig. 5). One example are pyridine *N*-oxides possessing amino acid as the part of the pendant chain **25** prepared by Benaglia et al. [64]. Other classes of pyridine *N*-oxides **26** and **27** with pendant amino acid chains were prepared by Laschat et al. [65].

The next group of *N*-oxides are those bearing the element of central chirality (Fig. 6). This group comprises various compounds such as pyridine *N*-oxide **28** prepared by Marchetti et al. (no absolute configuration was given) [60], Denmark et al. [66] reported a large series of chiral *N*,*N*′-dioxides **29** based on Bolm's catalysts scaffold [67, 68], *N*,*N*′-dioxides **30a** and **30b** prepared by Benaglia et al. [53], pyridine *N*-oxide **31a** and bipyridine *N*,*N*′-dioxide **31b** prepared by Boyd et al. [69], and finally *N*-oxides **32** and **33** were prepared by Ramanathan et al. [70, 71]. Stončius et al. [72] synthesized a series of *N*-oxides **34** and **35** in which the pyridine moieties were fused

with the bicyclo[3.3.1]nonane framework. Finally, pyridine *N*-oxide **36** having additional bis-sulfoxide moieties was prepared by Juaristi et al. [73]. Worth mentioning are also amylose and cellulose derivatives bearing pyridine *N*-oxide groups [74].

Regarding *N*-oxides possessing an element of planar chirality, only a handful of compounds have been synthesized so far (Fig. 7). The pioneering work was done by Fu et al. [75] who prepared ferrocene containing pyridine *N*-oxide **37**. In addition, *N*-oxides possessing the [2.2]-paracyclophane scaffold **38** and **39–41** were prepared by Andrus et al. [76] and Rowlands et al. [77], respectively. A similar situation concerns *N*-oxides possessing elements of helical chirality (Fig. 8). A series of various helical *N*-oxides **42–44** [78, 79] and **45** [80] was prepared by Takenaka et al. (Fig. 8).

The last group (Fig. 9) comprise chiral bipyridine *N*-oxide **46** [56] and *N*,*N*′-dioxide **47** [57] having elements of both central and axial chirality that were prepared by Kočovský et al., *N*,*N*′-dioxide **48** was prepared by Malkov et al. [81], and finally *N*,*N*′-dioxides **49** and **50** bearing the chiral tetrahydrofuranyl moiety by Kotora et al. [49, 50]. A large series of variously substituted axially chiral bipyridine *N*-oxides **51–55** was prepared by Denmark et al. [66, 82]. This group also comprises other types of chiral *N*,*N*′-dioxides possessing similar structural features [83].

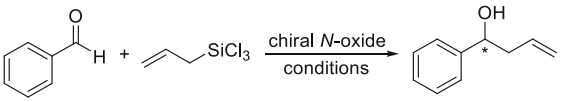
4.2 Allylations and Crotylations

N-Oxides of various types have been used as chiral Lewis bases able to activate Lewis acids (halosilanes), namely, in reactions of aldehydes with allyltrichlorosilane (Hosomi–Sakurai type allylations) providing chiral homoallylic alcohols. Their catalytic activity, i.e., increasing of the reaction rate and asymmetric induction, was usually tested in allylations of aromatic aldehydes. Allylation of benzaldehyde was usually chosen to assess the abovementioned properties. For typical examples, see the results summarized in Table 3. The outcome of the allylation usually depended on the amount of a catalyst and usually rather high loading such as 10 mol% with respect to the aldehyde and reaction times (24 or 48 h or more) were required to obtain a reasonable reaction rate and enantioselectivity. On the other hand, there exists a couple of *N*-oxides capable of catalyzing the reaction at a 1 mol% level providing the respective products in high yields and asymmetric induction within a reasonable period of time (1–6 h). Allylations of other benzaldehydes were studied as well and can be found elsewhere [84, 85].

A strong solvent effect on asymmetric induction as well as on the configuration of the homoallylic alcohol was observed during allylations catalyzed by **5**. Thus catalysis by (*R*)-**5** gave (*S*)-homoallylic alcohols in MeCN, CH_2Cl_2, $CHCl_3$, and other polar solvents; whereas its use in nonpolar solvents such as toluene, THF, chlorobenzene, etc. gave (*R*)-homoallylic alcohols [43]. Properties of (*S*)-**1d** were tested in allylation of 4-methoxybenzaldehyde only. It proceeded with a high enantioselectivity of 92% ee (66% yield) [43].

Another interesting and synthetically useful reaction is crotylation of aldehydes with (*E*)- and (*Z*)-crotyltrichlorosilanes. The former gives rise preferentially to *anti*

Table 3 Allylation of benzaldehyde catalyzed by various chiral *N*-oxides



Catalyst	mol (%)	Solvent	Conditions	Yield (%)[a]	ee (%)[a]	Ref
(*S*)-**1a**	10	CH_2Cl_2	23°C, 2 h	82	52	[40]
(*S*)-**1b**	10	CH_2Cl_2	−78°C, 6 h	85	88 (*R*)	[40]
(*R*)-**1c**	0.1	CH_2Cl_2	−45°C, 2.5 h	95	84 (*S*)	[41]
(*R*)-**2**	5	CH_2Cl_2	−40°C, 2 h	60	87 (*R*)	[45]
(*R*)-**3**	5	CH_2Cl_2	20°C, 72 h	50	20	[46]
(*S*)-**4a**	5	CH_2Cl_2	−78°C, 6 h	87	74 (*R*)	[47]
(*S*)-**4b**	5	CH_2Cl_2	−78°C, 6 h	53	72 (*R*)	[47]
(*S*)-**4c**	1	CH_2Cl_2	−78°C, 1 h	48	80 (*R*)	[48]
(*R*)-**5**	1	Toluene[b]	−78°C, 1 h	45	83 (*S*)	[49]
(*R*)-**6a**	1	CH_2Cl_2	−80°C, 16 h	88	95 (*S*)	[51]
(*R*)-**6b**	1	CH_2Cl_2	−80°C, 20 h	–	87 (*R*)	[52]
(*R*)-**7**	10	MeCN	−90°C, 24 h	22	40 (*R*)	[53]
9	7	CH_2Cl_2	−90°C, 24 h	67	92 (*S*)	[56]
10a	20	CH_2Cl_2	−60°C, 18 h	72	46 (*S*)	[57]
10b	20	CH_2Cl_2	−60°C, 18 h	75	88 (*S*)	[57]
10c	20	CH_2Cl_2	−60°C, 18 h	72	84 (*S*)	[57]
10d	10	CH_2Cl_2	−60°C, 18 h	15	97 (*S*)	[57]
11	10	CH_2Cl_2	−60°C, 18 h	90	22 (*S*)	[57]
12a	7	MeCN	−60°C, 18 h	66	41 (*S*)	[58]
12b	7	MeCN	−60°C, 18 h	15	16 (*S*)	[58]
12c	7	MeCN	−60°C, 18 h	20	7 (*S*)	[58]
12d	7	MeCN	−60°C, 18 h	55	68 (*S*)	[58]
12e	7	MeCN	−60°C, 18 h	51	67 (*S*)	[58]
13	5	MeCN	−40°C, 18 h	95	96 (*S*)	[59]
14	10	MeCN	0°C, 48 h	17	6 (*S*)	[60]
17	7	CH_2Cl_2	−90°C, 48 h	18	41 (*R*)	[56]
20	10	MeCN	−40°C, 67 h	37	95 (*S*)	[60]
21a	10	MeCN	−40°C, 72 h	30	4 (*S*)	[60]
21b	10	MeCN	−40°C, 72 h	24	35 (*S*)	[60]
22	10	MeCN	−40°C, 72 h	22	30 (*S*)	[60]
23	10	CH_2Cl_2	0°C, 3 h	89	74 (*R*)	[63]
25a	10	MeCN	20°C, 48 h	85	0	[64]
25b	10	MeCN	20°C, 48 h	53	6	[64]
25c	10	MeCN	0°C, 48 h	45	68	[64]
25d	10	MeCN	−20°C, 48 h	40	67 (*S*)	[64]
25e	10	MeCN	0°C, 48 h	50	60 (*S*)	[64]
30a	10	MeCN	−45°C, 40 h	60	50 (*S*)	[53]
30b	10	MeCN	−45°C, 40 h	50	35 (*S*)	[53]
31a	10	CH_2Cl_2	0°C, 24 h	60	35 (*R*)	[69]

(continued)

Table 3 (continued)

Catalyst	mol (%)	Solvent	Conditions	Yield (%)[a]	ee (%)[a]	Ref
31b	10	CH_2Cl_2	−78°C, 12 h	64	26 (*R*)	[69]
32	20	$CHCl_3/(CH_2Cl)_2$	−78°C, 24 h	87	83 (*S*)	[70]
38	1.5	MeCN	−40°C, 6 h	95	93 (*S*)	[76]
39a	10	CH_2Cl_2	−78°C	65	38 (*R*)	[76]
39b	10	CH_2Cl_2	−78°C	52	36 (*S*)	[76]
41a	10	CH_2Cl_2	−78°C	72	28 (*S*)	[77]
41b	10	CH_2Cl_2	−78°C	58	30 (*S*)	[77]
46	10	CH_2Cl_2	−60°C, 12 h	72	98 (*S*)	[56]
47	10	CH_2Cl_2	−60°C, 12 h	52	14 (*S*)	[57]
(*R*,*R*,*R*)-**49**	1	MeCN	−40°C, 1 h	100	48 (*S*)	[49]
(*S*,*R*,*R*)-**49**	1	PhCl	−40°C, 1 h	100	62 (*S*)	[49]
(*R*,*R*)-**50**	1	THF	−78°C, 1 h	100	93 (*S*)	[50]
(*S*,*R*)-**50**	1	THF	−78°C, 1 h	98	96 (*S*)	[50]

[a]Configuration of the obtained alcohol is given in parentheses
[b]Allylations in other solvents were tested as well

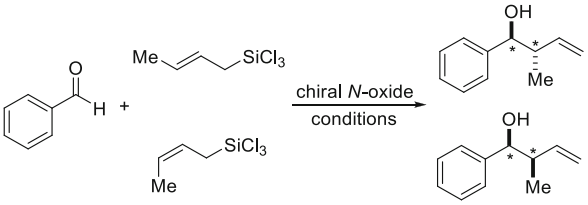
whereas the latter affords *syn* products. Typical examples of benzaldehyde crotylations are displayed in Table 4. Crotylations of other substrates were reported as well [90]. A more detailed kinetic and computational investigation of the catalytic enantio- and diastereoselective allylation and crotylation is given elsewhere [91].

Allylation of α,β-unsaturated aldehydes has also been extensively studied. In the majority of the cases, only allylation of cinnamaldehyde and its substituted congeners was studied [40, 42, 45, 51, 56, 57, 60, 70, 81, 86, 88, 89, 92, 93]. More systematic studies were carried out in a handful of cases only [94–96]. Worth mentioning is also allylation (crotylation) of β-haloacrylaldehydes, products of which could be used as convenient chiral building blocks [97, 98]. Only a handful examples have been reported for allylations of α,β,γ,δ-unsaturated aldehydes and these mainly concerned reactions catalyzed by **12** [96], by (*R*,*R*) and (*S*,*R*)-**50** [97, 99, 100], or by (*R*,*R*,*R*)- and (*S*,*R*,*R*)-**49** [100]. Allylation of aliphatic aldehydes catalyzed by **5**, (*S*,*R*,*R*)-**49** [101] and (*S*,*R*)-**50** [102] was tested as well, but asymmetric induction was rather low and did not exceed 68% ee.

4.3 Propargylations and Allenylations

Selective propargylation and allenylation of aromatic aldehydes with propargyltrichlorosilane and allenyltrichlorosilane in the presence of 20 mol% of chiral *N*,*N*′-dioxide (S)-**1b** were reported by Denmark et al. [103]. Propargyltrichlorosilane and allenyltrichlorosilane were prepared in situ by a reaction of trichlorosilane with propargyl chloride either under Cu or Ni catalysis, respectively. Although it was the first example,

Table 4 Crotylations of benzaldehyde catalyzed by various chiral *N*-oxides



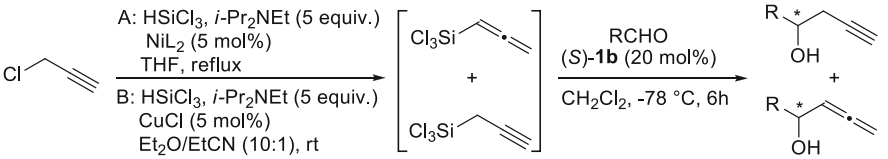
Catalyst	mol (%)	*trans* or *cis*	Solvent	Conditions	Yield (%)[a]	*anti*/*syn*	ee (%)[a] *anti*, *syn*	Ref
(*S*)-**1b**	10	trans	CH_2Cl_2	−78°C, 6 h	68	97:3	86 (1*R*,2*R*)	[40]
(*S*)-**1b**	10	cis	CH_2Cl_2	−78°C, 6 h	64	1:99	84 (1*R*,2*S*)	[40]
(*S*)-**1c**	10	trans	MeCN	−45°C, 2.5 h	84	96:4	73 (1*S*,2*S*)	[86]
(*S*)-**1c**	10	cis	MeCN	−45°C, 2.5 h	82	1:99	77 (1*S*,2*R*)	[86]
(*R*)-**2**	5	trans	CH_2Cl_2	−40°C	54	93:7	87	[45, 87]
(*S*)-**2**	5	trans	CH_2Cl_2	−40°C, 24 h	65	95:5	66 (1*S*,2*S*), 77 (1*S*,2*R*)	[88]
(*S*)-**2**	5	cis	CH_2Cl_2	−40°C, 24 h	78	1:99	69 (1*S*,2*S*), 79 (1*S*,2*R*)	[88]
(*R*)-**6a**	1	trans	CH_2Cl_2	−80°C, 16 h	64	86:14	94 (1*S*,2*S*), 95	[89]
9	7	trans	CH_2Cl_2	−40°C	70	68:32	65/78	[45]
(−)-**10d**	10	trans	MeCN	−40°C, 18 h	88	98:2	98	[57]
(−)-**10d**	10	cis	MeCN	−40°C, 18 h	37	10:90	87	[57]
25c	1	trans/cis, 8/2	MeCN	0°C, 48 h	40	80:20	69	[64]
(*R*,*R*)-**50**	1	trans	PhCl	−40°C, 24 h	82	71:29	91/87	[50]

[a]Configuration of the obtained alcohol is given in parentheses

a high catalyst loading, moderate yields, and enantioselectivity were short of expectations (Table 5).

Later, Takenaka et al. developed a highly enantioselective synthesis of homopropargylic alcohols by using a new helical chiral *N*-oxide catalyst **45** and allenyltrichlorosilane (Table 6) [80, 104]. Reactions with various aldehydes provided the corresponding homopropargylic alcohols in high yields and with high enantioselectivity, when 10 mol% catalyst loading was used. The reaction tolerates functionalities in the arene, such as halogen, nitro, trifluoromethyl, and methoxy groups. However, the reaction of cyclohexylcarbaldehyde afforded the product in a lower yield and with a moderate enantioselectivity. In addition, this method was used for enantio- and regioselective propargylation of *N*-acylhydrazones (Scheme 4).

Table 5 Selective synthesis of optically active allenyl and homopropargyl alcohols



Entry	Method	Aldehyde	Yield (%)[a]	Propargyl:allenyl[b]	ee (%)[c, d]	Configuration[e]
1	A	Ph	65	>30:1	52	*R*
2	A	4-$MeOC_6H_4$	62	>30:1	40	*R*
3	A	4-ClC_6H_4	49	>30:1	46	*R*
4	A	$Ph(CH_2)_2$	35	>30:1	23	*R*[f]
5	B	Ph	72	1:15	54	*R*
6	B	4-$MeOC_6H_4$	76	1:9	62	*R*[f]
7	B	4-ClC_6H_4	48	1:9	49	*R*[f]
8	B	$Ph(CH_2)_2$	44	1:10	22	*R*[f]

[a]Combined isolated yields
[b]Determined by ^1H NMR
[c]Enantiomeric excess of the major isomer
[d]Determined by HPLC
[e]Assigned by comparison with optical rotation and/or retention time on chiral HPLC
[f]Assigned by analogy

The initial idea on the supposed origin of high enantioselectivity based on π–π-stacking between the phenyl ring of the aromatic aldehyde and the helical core of the catalyst was corrected later by the theoretical study of Wheeler and coworkers. They reported a computational study showing that simple electrostatic interactions stabilize the preferred *Si* face addition [105].

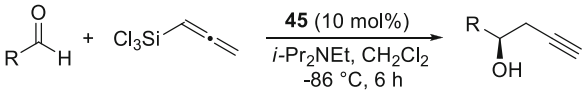
4.4 Aldol Reactions

4.4.1 Aldol Reaction with Ketones

Compared to the multitude of Lewis acid-catalyzed enantioselective aldol additions, the Lewis base catalysis is considerably scarce. Concerning the Lewis base catalysts, chiral phosphoramides introduced by Denmark et al. have been studied most extensively. In 2002, he reported the application of chiral *N*-oxide catalysis for aldol addition to unactivated ketones [61, 66], which, unlike an addition to aldehydes, is a considerably more challenging reaction, and therefore a general solution was lacking. Using highly reactive trichlorosilyl ketene acetals[1] enabled to overcome the diminished electrophilicity and increased steric hindrance of ketones compared to aldehydes. It is

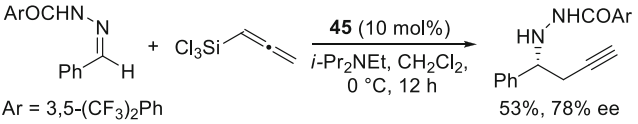
[1]Trichlorosilyl enolates of aldehydes and ketones as the reagents of the first choice were found not reactive enough for addition to ketones.

Table 6 Asymmetric propargylation of aldehydes catalyzed by helically chiral *N*-oxide **45**



Entry	R	Yield (%)[a]	ee (%)[b]
1[c]	Ph	87	86
2[c]	2-Naphthyl	86	84
3[c]	4-Br-C_6H_4	95	92
4	4-Cl-C_6H_4	90	92
5	4-F-C_6H_4	93	88
6[d]	4-NO_2-C_6H_4	55[e]	92
7	4-CF_3-C_6H_4	80	90
8	4-MeO-C_6H_4	80	74
9	4-Me-C_6H_4	85	82
10[c]	2-Br-C_6H_4	93	96
11	2-Cl-C_6H_4	97	96
12	2-F-C_6H_4	98	92
13	2-NO_2-C_6H_4	87	96
14[d]	2-CF_3-C_6H_4	95	94
15	2-MeO-C_6H_4	78	94
16	2-Me-C_6H_4	90	86
17[d]	2-Br-4-Me-C_6H_4	92	96
18[f]	Cy	61[g](80)[h]	59

[a]Isolated yield
[b]Determined by HPLC
[c]Absolute configurations were determined
[d](*M*)-**43** catalyst was used
[e]Low yield is presumably due to a poor solubility of the aldehyde
[f](*R*)-isomer is major
[g]12 h
[h]36 h

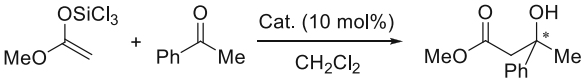


Scheme 4 Propargylation of an acylhydrazone catalyzed by **45**

worth mentioning that enantioselectivities reached with chiral pyridine *N*-oxides were superior to those obtained with the aforementioned phosphoramides. Vast effort was undertaken to optimize properties of the *N*-oxide catalysts (Table 7).

It was concluded that the asymmetric inductions and yields of the aldol product obtained with at-that-time-known monomeric **15** and dimeric axially chiral **19** or centrally chiral catalysts (*R*)-**1a** and (*S*)-**1g** are overcome by pyridine *N*-oxides **29a** and

Table 7 Enantioselective aldol addition to ketone – *N*-oxide catalysts optimization

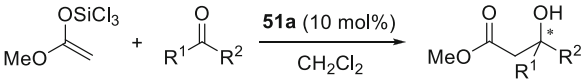


Entry	Catalyst	Temp. (°C)	Yield (%)	ee (%)	References
1	**15**	0	55	3	[60]
2	**19**	0	15	<1	[60]
3	(*R*)-**1a**	0	45	45	[65]
4	(*S*)-**1g**	0	39	26	[65]
5	**29a**	0	92	55	[65]
6	**29b**	0	94	64	[65]
7	(*P*)-**51a**	0	90	74 (*S*)	[65]
8	(*P*)-**51a**	−20	94	82 (*S*)	[65]
9	(*M*)-**51a**	−20	89	42 (*R*)	[65]
10	**51b**	−20	89	82 (*S*)	[60]
11	**51c**	−20	91	87 (*S*)	[60]
12	**51d**	−20	64	60 (*S*)	[60]
13	**51e**	−20	88	74 (*S*)	[60]
14	**51f**	−20	91	1 (*R*)	[60]
15	**52b**	−20	93	64 (*S*)	[60]
16	**52a**	−20	90	80 (*S*)	[60]
17	**52c**	−20	87	47 (*S*)	[60]
18	**53a**	−20	32	61 (*S*)	[60]
19	**53b**	−20	95	72 (*S*)	[60]
20	**54**	−20	93	72 (*S*)	[60]
21	**55**	−20	92	24 (*S*)	[60]
22	**55**	−20	94	5 (*R*)	[60]

29b derived from the Bolm's ligand. A significant improvement of enantioselectivity was reached by blocking the rotation along the C2–C2′ bond by installing methyl groups in positions 3 and 3′. Thus the presence of the enantioselectivity-attenuating axial conformer of the catalyst was avoided, and catalysts **51** and **52** demonstrated the synergy of central and axial chirality (compare Entries 8 and 9 with Entry 7). Regarding the steric influences, the best selectivity was obtained with catalyst **51c** possessing *tert*-butyl and 2,4,6-trimethylbenzyl groups. With respect to the electronic influences, the decreased yield was obtained with catalyst **53a** clearly indicating that electron deficient pyridine *N*-oxides (weaker Lewis bases) are less capable of catalyzing the reaction.

The study aiming to determine the scope of the reaction revealed that the greater the difference in R^1 and R^2 bulkiness is, the higher enantioselectivities are obtained (Table 8). Furthermore, aldol condensation with aromatic ketones (Entries 1–9) resulted in higher enantioselectivities than with the aliphatic ones, whether linear, cyclic, branched, or conjugated (Entries 10–16).

Table 8 The scope of the pyridine *N*-oxide catalyzed aldol addition with respect to various ketones



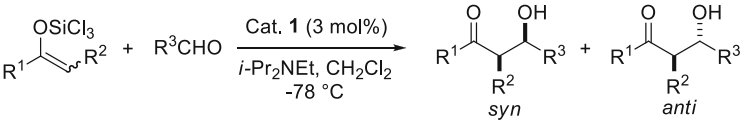
Entry	Ketone	Yield (%)	ee (%)
1	PhCOMe	96	83
2	PhCOEt	90	81
3	PhCOC≡CH	89	86
4	1-Tetralone	90	80
5	1-NaphtylCOMe	89	56
6	2-FurylCOMe	87	49
7	PhC≡CCOMe	94	35
8	*p*-$CF_3C_6H_4COMe$	91	76
9	*p*-$MeOC_6H_4COMe$	94	68
10	(*E*)-PhCH=CHCOMe	87	11
11	2-Cyclohexenone	86	8
12	EtCOMe	84	32
13	$PhCH_2CH_2COMe$	97	35
14	cyclopropylCOMe	84	20
15	cyclohexylCOMe	91	32
16	*t*-BuCOMe	87	43

4.4.2 Aldol Reaction with Aldehydes

Nakajima et al. noticed that addition of trichlorosilyl enolates is analogous to the previously studied additions of allyltrichlorosilane to aldehydes and therefore a similar mechanism and enantioselectivities to those of the allylation reactions could be expected in the presence of *N*-oxide catalysts (Table 9) [54]. It was discovered that: (a) the aldolizations are high-yielding except for aliphatic aldehyde (Entry 11); (b) unlike Lewis acid-catalyzed reactions it is stereospecific, turning *E* enolates into *syn* aldol products and *Z* enolates into *anti* ones (Entries 3–10), and (c) the asymmetric induction in the presence of catalysts (*R*)-**1a** or (*R*)-**1g** strongly depended on the substrate and catalyst structure.

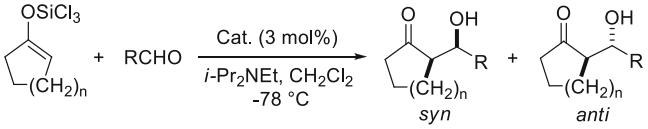
In the case of trichlorosilyl enolates of cyclic ketones, modest enantioselectivities were observed, when bidentate catalysts (*R*)-**1a** and (*R*)-**1g** were used (Table 10); nevertheless, the diastereoselectivity followed the previous pattern yielding predominantly the *anti*-products [54]. However, employing monodentate catalysts (*R*)-**2** and (*R*)-**8** led to isolation of *syn* products with somewhat higher enantioselectivity.

Table 9 Aldol addition of trichlorosilyl enolates of acyclic ketones to aldehydes catalyzed by **1**



Entry	R^1	R^2	*E*/*Z*	R^3	Catalyst	Yield (%)	*syn*/*anti*	ee (%) *syn*, *anti*
1	Ph	H	–	Ph	(*R*)-**1g**	85	–	<5
2	Ph	H	–	Ph	(*R*)-**1a**	87	–	<5
3	H	C_5H_{11}	12/1	Ph	(*R*)-**1g**	96	1/11	6, 7
4	H	C_5H_{11}	12/1	Ph	(*R*)-**1a**	86	1/12	81, 23
5	H	C_5H_{11}	1/4	Ph	(*R*)-**1g**	88	3/1	9, 12
6	H	C_5H_{11}	1/4	Ph	(*R*)-**1a**	90	4/1	79, 23
7	Ph	Me	1/10	Ph	(*R*)-**1g**	82	7/1	82, 33
8	Ph	Me	1/10	Ph	(*R*)-**1a**	88	9/1	6, <5
9	Ph	Me	1/10	4-$MeOC_6H_4$	(*R*)-**1g**	86	15/1	67, 13
10	Ph	Me	1/10	PhCH=CH	(*R*)-**1g**	59	15/1	63, 43
11	Ph	Me	1/10	$PhCH_2CH_2$	(*R*)-**1g**	Trace	–	–

Table 10 Aldol addition of trichlorosilyl enol ethers of cyclic ketones to aldehydes



Entry	*n*	R^3	Catalyst	Yield (%)	*syn*/*anti*	ee (%) *syn*, *anti*
1	2	Ph	(*R*)-**1g**	80	1/10	39, 30
2	2	Ph	(*R*)-**1a**	94	1/3	21, 30
3	2	Ph	(*R*)-**2**	92	8/1	<5, 30
4	2	Ph	(*R*)-**8**	92	25/1	47, 60
5	3	Ph	(*R*)-**8**	93	30/1	50, 11
6	1	Ph	(*R*)-**8**	94	13/1	62, 66
7	1	4-$MeOC_6H_4$	(*R*)-**8**	90	14/1	63, 55
8	1	4-$CF_3C_6H_4$	(*R*)-**8**	98	14/1	72, 69
9	1	PhCH=CH	(*R*)-**8**	93	4/1	28, 42
10	1	$PhCH_2CH_2$	(*R*)-**8**	22	1/1	50, 40

4.4.3 Reductive Aldol Addition

Nakajima et al. also reported a highly *syn*-selective reductive aldol reaction of an α,β-unsaturated ketone – chalcone – with benzaldehyde [106]. 1,4-Reduction of the ketone by trichlorosilane in the presence of a pyridine *N*-oxide catalyst gave rise selectively to a (*Z*)-trichlorosilyl enolate. Once the highly pure (*Z*)-enolate was formed (due to the cyclic transition state), the *N*-oxide catalyst facilitated the enantioselective addition to a carbonyl acceptor. The use of (*R*)-**1a** and (*R*)-**1g** catalysts gave rise to the

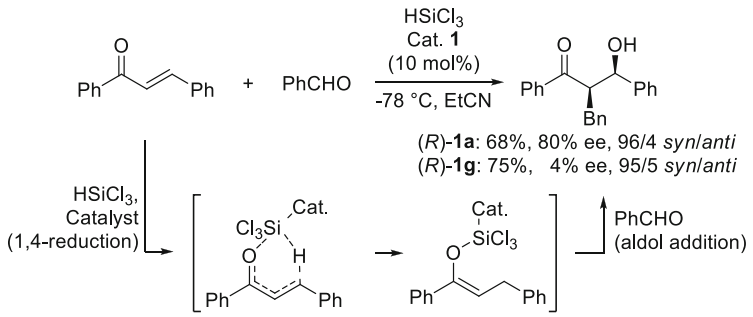
aldol products with comparably high diastereoselectivity (~19/1), while a satisfactory asymmetric induction of 80% ee was obtained only in the case of the former catalyst (Scheme 5). An intramolecular reaction was reported as well, the yield and selectivity were moderate (Scheme 6).

4.5 Alkylations

There is only one example of *N*-oxide catalyzed alkylation of aldehydes and it was reported by Laschat et al. [65]. They used pyridine *N*-oxides **26** and **27** possessing amino acid moieties as catalysts for alkylations of benzaldehyde with diethylzinc (Table 11). The reaction proceeded with good yields of the homoallyl alcohols in the range of 37–92%, but with a rather poor enantioselectivity in the range of 2–29% ee.

4.6 Epoxide Cleavage

Epoxide cleavage with various electrophiles leads to the formation of chiral alcohols. The selected examples are shown in Table 12. The first chiral Lewis base catalyzed epoxide ring cleavage was reported by Fu et al. in 2001. He studied cleavage of symmetrically substituted epoxides with tetrachlorosilane catalyzed by a ferrocene containing pyridine *N*-oxide **37**. The reaction proceeded usually with a high enantioselectivity (91–98% ee) for aryl substituted epoxides [75]. Takenaka et al. studied catalytic activity of several helically chiral *N*-oxides **42–44** [78]. Out of these, the use of **44** gave products



Scheme 5 Intermolecular enantioselective tandem 1,4-reduction-aldol additions catalyzed by (*R*)-**1**

Scheme 6 An intramolecular enantioselective tandem 1,4-reduction-aldol addition catalyzed by (*R*)-**1g**

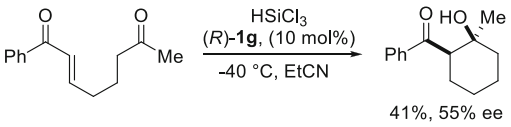
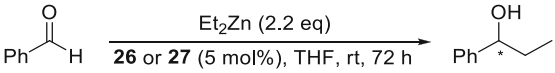


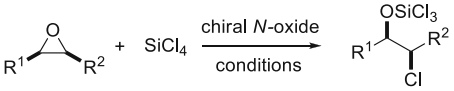
Table 11 Alkylation of benzaldehyde catalyzed by **26** and **27**



Catalyst	Yield (%)	ee (%)[a]
26a	52	16 (*S*)
26b	37	12 (*S*)
26c	37	2 (*S*)
26d	71	9 (*S*)
27a	71	11 (*S*)
27b	88	7 (*S*)
27c	92	29 (*S*)
27d	88	8 (*R*)

[a]Determined by GC

Table 12 Ring opening of symmetrically substituted epoxides by various *N*-oxide catalysts



Catalyst	mol (%)	R^1, R^2	Solvent	Conditions	Yield (%)	ee (%)[a]
37	5	Ph	CH_2Cl_2	−85°C	88	94
37	5	4-FC_6H_4	CH_2Cl_2	−85°C	97	91
37	5	4-MeC_6H_4	CH_2Cl_2	−85°C	94	93
37	5	4-$CF_3C_6H_4$	CH_2Cl_2	−85°C	93	98
37	5	2-naphtyl	CH_2Cl_2	−85°C	84	94
37	5	CH_2OBn	CH_2Cl_2	−85°C	91	50
44	10	Ph	CH_2Cl_2	−78°C, 6 h	77	94
44	10	2-naphtyl	CH_2Cl_2	−78°C, 6 h	84	92
44	10	4-ClC_6H_4	CH_2Cl_2	−78°C, 6 h	83	94
44	10	4-MeC_6H_4	CH_2Cl_2	−78°C, 6 h	83	92
44	10	4-$CF_3C_6H_4$	CH_2Cl_2	−78°C, 6 h	63	87
44	10	$CH_2O(CH_2)_3Ph$	CH_2Cl_2	−78°C, 6 h	64	72
33	0.5	Ph	$CHCl_3$	−30°C, 2 h	94	93 (1*R*,2*R*)
33	0.5	4-FC_6H_4	$CHCl_3$	−30°C, 1.7 h	92	89 (1*S*,2*S*)
33	0.5	4-MeC_6H_4	$CHCl_3$	−30°C, 3 h	97	78 (1*S*,2*S*)
33	0.5	3-$MeOC_6H_4$	$CHCl_3$	−30°C, 1.5 h	96	89(1*R*,2*R*)
(*R*,*R*,*R*)-**49**	5	Ph	THF	−78°C, 24 h	76	65
(*S*,*R*,*R*)-**49**	5	Ph	THF	−78°C, 24 h	74	69

[a]Determined by GC

with the highest asymmetric induction. Another contribution to this area comes from Ramanathan et al. [71], who used conformationally rigid bipyridine *N*,*N*′-dioxide **33** as the catalyst. Comparison of catalytic activity of **49** and **50** revealed that the former gave

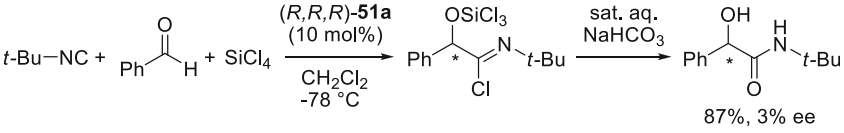
better results (higher enantioselectivity) than the latter one, albeit its activity could not match the previously published results [107]. In a similar manner, *N*-oxides with the bicyclo[3.3.1]nonane framework gave in general products with low enantiopurity [72].

4.7 α-Addition of Isocyanides to Aldehydes (Passerini-Type Reaction)

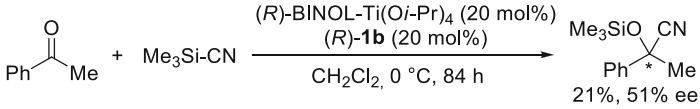
In principle, the Passerini reaction could be also carried out under Lewis acid catalysis, but several problems were recognized in individual steps. However, these problems could be circumvented by the use of the concept of the Lewis base activation of Lewis acids. The main feature of this reaction is the activation of a weak Lewis acid, $SiCl_4$, by a weak chiral Lewis base generating a highly reactive and selective siliconium ion that reacts with an aldehyde. The ensuing reaction steps then give rise to an imidoyl chloride that after hydrolysis forms the expected product – a hydroxy amide. It has been shown that this reaction could be catalyzed by chiral bisphosphoramides to give highly enantioenriched products. Also *N*,*N*′-dioxide (*R*,*R*,*R*)-**51a** possessing elements of central and axial chirality was tested, but, disappointingly, its use did not show any sensible enantioselectivity. Thus the reaction of *tert*-butyl isocyanide **2**, benzaldehyde **3**, and tetrachlorosilane catalyzed by **51a** gave the corresponding α-hydroxy amide in a very good yield of 87% but with the poor enantioselectivity of 3% ee (Scheme 7) [29].

4.8 Addition of Me_3Si-CN to Ketones and Related Compounds (Strecker Reaction)

Addition of trimethylsilyl cyanide to acetophenone catalyzed by dual Lewis acid/Lewis base system composed of (*R*)-BINOL-Ti(O*i*-Pr)$_4$/(*R*)-**1b** was studied as a part of mechanistic studies by Feng et al. [108]. Comparison of the reaction carried out in the presence of racemic and chiral Lewis bases showed differences in enantioselectivity (43 and 51% ee) indicating a positive effect of the chiral Lewis base on asymmetric induction (Scheme 8). Addition of trimethylsilyl cyanide to aldimines promoted by various chiral *N*-oxides was studied as well [109] (for theoretical studies, see: Su et al.



Scheme 7 Passerini-type reaction catalyzed by **51a**



Scheme 8 Trimethylsilyl cyanide addition to acetophenone catalyzed by (*R*)-**1b**

[110]). However, in order to achieve a high asymmetric induction (up to 95% ee), the presence of stoichiometric amount of the chiral *N*-oxide was required.

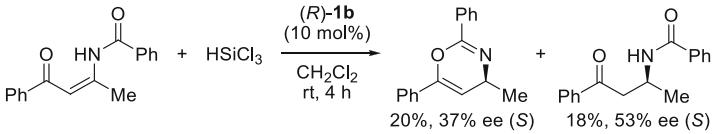
4.9 Reductions

Reductions catalyzed by chiral pyridine *N*-oxide are rather rare. There is one example reported by Nakajima et al., who studied reduction of *N*-acylated β-amino enones (Scheme 9) [111]. Reduction of *N*-benzoyl enone by $HSiCl_3$ catalyzed by (*R*)-**1b** gave a mixture of 4*H*-1,3-oxazine (20%) and keto amide (18%) but with a rather low enantioselectivity of 37 and 53% ee, respectively.

The second example of reduction catalyzed by chiral pyridine *N*-oxide was reported by Laschat et al., who reported the reduction of ketones by $BH_3{\cdot}SMe_2$ in the presence of pyridine *N*-oxides **26** or **27** [65]. The reductions were carried out with just three ketones. The corresponding alcohols were obtained in very good yields, but with a low or moderate enantioselectivity, in the range of 7–64% (Table 13). The highest enantioselectivity (64% ee) was observed in the reduction of α-chloroacetophenone catalyzed by the monosubstituted catalyst **26d** (Entry 4).

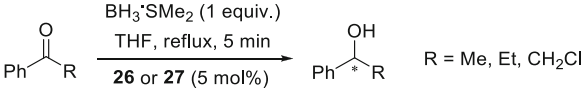
4.10 Rearrangements

There is only one report on a rearrangement catalyzed by a chiral pyridine *N*-oxide. It concerns the synthesis of thiols via a rearrangement of carbonodithioic *O,S*-esters to carbonodithioic *S,S*-esters followed by transformation into thiols [112]. The rearrangement was studied in the presence of a terpene based pyridine *N*-oxide **16** and nicotine derived *N,N′*-dioxide **24** (Scheme 10). The use of the former did not result in any measurable asymmetric induction and the latter provides the corresponding thiols with a rather low enantioselectivity of 37.7% ee for the butane-2-thiol and 11.4% ee for the 1-phenylethylthiol.



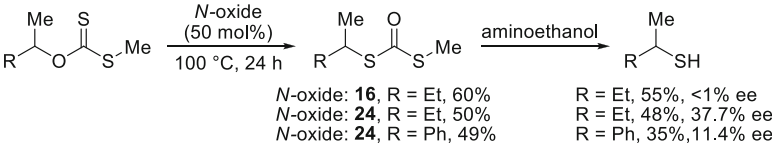
Scheme 9 Reduction of *N*-benzoyl enone by (*R*)-**1b**

Table 13 Reductions of ketones catalyzed by **26** and **27**



		R = Me		R = Et		R = CH_2Cl	
Entry	Catalyst	Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	**26a**	99	7 (*R*)	98	8 (*R*)	99	20 (*S*)
2	**26b**	99	11 (*R*)	99	17 (*R*)	97	21 (*S*)
3	**26c**	99	7 (*R*)	99	12 (*R*)	99	16 (*S*)
4	**26d**	99	20 (*R*)	98	21 (*R*)	99	64 (*S*)
5	**27a**	97	9 (*R*)	98	9 (*R*)	99	21 (*S*)
6	**27b**	99	10 (*R*)	99	16 (*R*)	99	33 (*S*)
7	**27c**	99	32 (*R*)	99	38 (*R*)	99	37 (*S*)
8	**27d**	99	31 (*R*)	99	33 (*R*)	98	51 (*S*)

[a]Isolated yields
[b]Determined by capillary GC



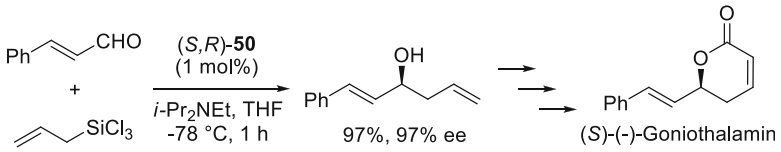
Scheme 10 Rearrangement of carbonodithioic *O*,*S*-esters to carbonodithioic *S*,*S*-esters by **16** and **24** (ee's were determined by optical rotation)

5 *N*-Oxide Catalyzed Reactions in Syntheses of Natural Compounds

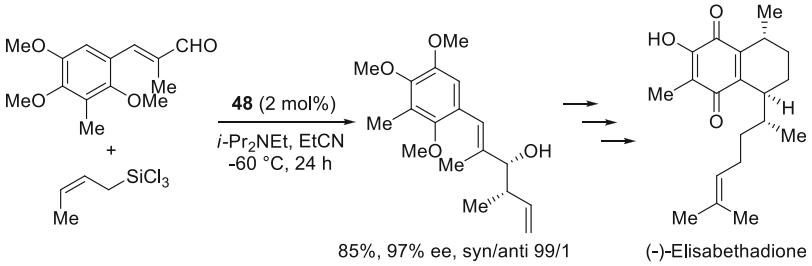
Out of a huge number of chiral *N*-oxides, only a handful of them was used as catalysts for preparation of chiral building blocks that served as advanced intermediates for syntheses of natural or biologically active substances. Nonetheless several published examples nicely demonstrate their synthetic potential.

5.1 Naturally Occurring Compounds

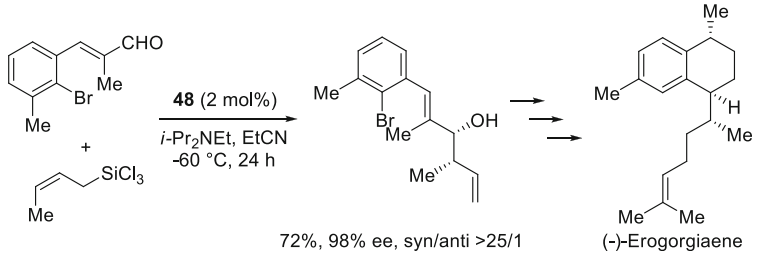
Several chiral *N*,*N*′-dioxides were used to catalyze processes that led to the formation of chiral intermediates applied in syntheses of natural products. Interestingly, most of them were applied in enantioselective allylation of various unsaturated aldehydes. Thus, allylation of cinnamaldehyde with allyltrichlorosilane catalyzed by (*S*,*R*)-**50** was used as a crucial step in the synthesis of goniothalamin [94] (Scheme 11). In a similar manner, **48** was used to catalyze a highly enantioselective *syn* crotylation of substituted cinnamaldehydes with (*Z*)-crotyltrichlorosilane. The crotylation products were used to synthesize (−)-elisabethadione [81] and (−)-erogorgiaene [93] (Schemes 12 and 13). Allylation of an α,β,γ,δ-dienal with allyltrichlorosilane catalyzed by (*S*,*R*)-**50** was used to prepare the known left-hand fragment of papulacandin D (Scheme 14) [100]. The same approach was used for the total synthesis of (+)-pteroenone that was based on *anti*-crotylation of 2,4-dimethylhexa-2,4-dienal with (*E*)-crotyltrichlorosilane (Scheme 15) [99]. Alternatively, *anti*-crotylation of (*E*)-3-iodomethacryldehyde was



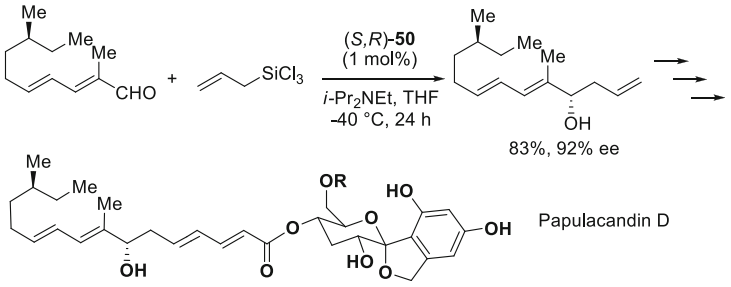
Scheme 11 Synthesis of (*S*)-(−)-goniothalamin



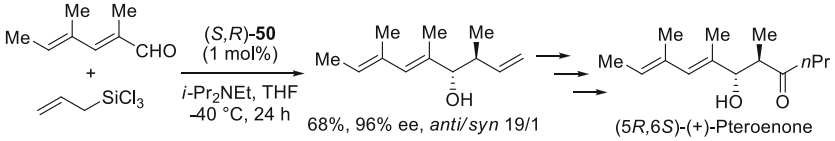
Scheme 12 Synthesis of (−)-elisabethadione



Scheme 13 Synthesis of (−)-erogorgiaene



Scheme 14 Synthesis of the left-hand fragment of papulacandin D



Scheme 15 Synthesis of pteroenone

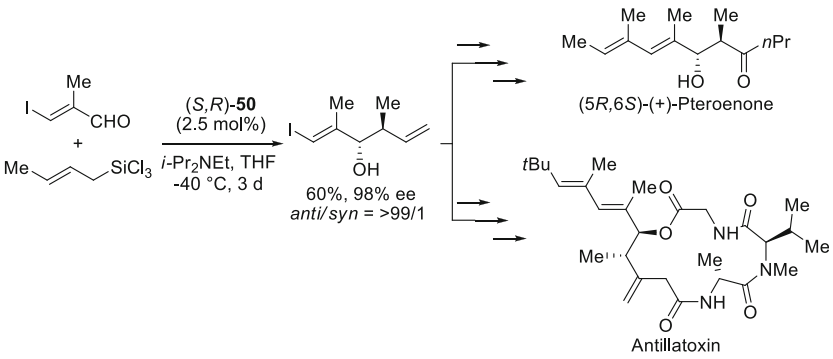
used to provide the advanced intermediate for the syntheses of pteroenone and antillatoxin (Scheme 16) [97]. Enantioselective allylation was also exploited in the synthesis of one of the chiral building blocks utilized in the synthesis of the callyspongiolide fragment [113]. Allylation of 6-heptenal catalyzed by (*S*,*R*)-**50** was tested as a route to a chiral intermediate for the coibacin D synthesis, but the achieved enantioselectivity was low (58% ee) [102].

5.2 Other Bioactive Substances

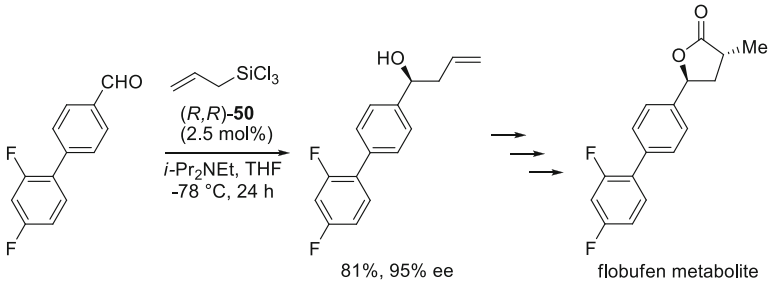
Allylation of 2′,4′-difluorobiphenyl-4-carbaldehyde with allyltrichlorosilane catalyzed by (*S*,*R*)-**50** was exploited in the synthesis of the flobufen metabolite (Scheme 17) [114]. Optionally, allylation of benzaldehyde under the same conditions could be also used for a synthesis of dapoxetine [114]. Analogously, allylation of 2-thiophenecarbaldehyde with allyltrichlorosilane catalyzed by (*S*,*R*)-**50** was the basis for a new synthesis of duloxetine (Scheme 18) [115].

6 Conclusion

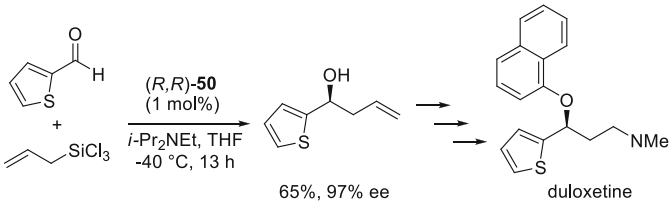
There is no doubt that achiral and chiral compounds possessing the pyridine *N*-oxide moiety could participate as catalysts in a wide range of organocatalyzed asymmetric reactions under rather mild reaction conditions. A rather large versatility of these catalysts in promoting both traditional reactions and, especially, new asymmetric reactions



Scheme 16 Synthesis of (+)-pteroenone and antillatoxin



Scheme 17 Synthesis of the flobufen metabolite



Scheme 18 Synthesis of duloxetine

is rewarding. The practical benefits of these reactions, especially in the area of asymmetric synthesis, include excellent enantioselectivity and activity providing useful chiral synthons with high enantiopurity, the use of cheap and readily available materials, mild reaction temperatures, operational simplicity, and last but not least, applicability in syntheses of natural or pharmaceutically active substances. There is no doubt that the future of the *N*-oxide family of catalysts, primarily in asymmetric transformations, is promising and will become one of the standard chemical tools in the field of organic synthesis.

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