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Chiral *N*-Oxides in Asymmetric Catalysis

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This microreview highlights the utilization of chiral amine *N*-oxides in catalytic asymmetric transformations, which are discussed in a more general context of catalysis by chiral Lewis bases. Both metal-free and metal-mediated reactions are surveyed.

1. Introduction

Homochiral compounds with heteroatoms displaying donor properties have long been recognized as suitable entities for ligand design.[1] At the same time, amine *N*-oxides, despite their pronounced nucleophilic character, remained in the shadows and have only made a visible impact in the field of asymmetric catalysis in the last decade. The use of pyridine-derived *N*-oxides was summarized recently,[2] and this microreview provides an update on the latest developments in the application of chiral *N*-oxides derived from tertiary amines and pyridines in asymmetric catalysis.

The applications of chiral *N*-oxides can be divided into two main groups. The first, currently experiencing a surge in activity, includes metal-free catalytic transformations mostly associated with organosilicon chemistry, while the second group comprises the methods in which *N*-oxides serve as ligands in transition metal catalysts.

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2. Metal-Free Transformations

The high nucleophilicity of the oxygen in *N*-oxides, coupled with a high affinity of silicon for oxygen (the strength of the Si–O bond in Me_3SiOMe is 114 kcal mol^{-1}, second only to the Si–F bond in Me_3SiF, which is 159 kcal mol^{-1}[3]) represents an ideal combination for the development of synthetic methodology based on nucleophilic activation of organosilicon reagents.[4]

2.1. Allylation of Aldehydes

Thanks to their operational simplicity, Lewis base catalyzed asymmetric allylations of aldehydes **1** with allyltri-

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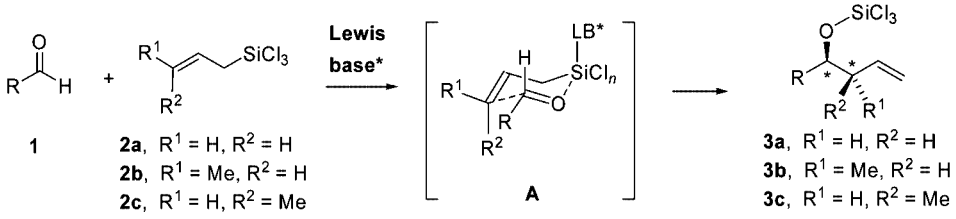
Pavel Kočovský was born in 1951 in Rychnov nad Kněžnou, Czechoslovakia (now Czech Republic), and in the same year the family moved to Prague, where he was raised and educated. He received an MSc in 1974 from the Technical University, Prague, where he did his diploma work with Prof. O. Červinka in the area of asymmetric reactions. He obtained a PhD in 1977 from the Czechoslovak Academy of Sciences, Institute of Organic Chemistry and Biochemistry, Prague, where he worked on steroid chemistry under the guidance of Dr. V. Černý and Prof. F. Šorm. He was then appointed to his first academic position at the same Institute, and stayed for another twelve years. During this period, he also taught various advanced courses at Charles University, Prague. In 1983 he obtained permission to leave Czechoslovakia temporarily and joined Prof. J. E. McMurry at Cornell University, Ithaca, NY, USA, as a research associate (1983–1984). He returned to his position in Prague in 1984 and later spent a sabbatical year with Prof. J.-E. Bäckvall at the University of Uppsala, Sweden (1989–1990). In January 1991 he moved to the UK and started a new academic career, first at the University of Leicester, where he spent almost nine years, obtained a DSc (1993), and rose in the ranks to full professor. In 1999 he moved to the University of Glasgow as the Sir William Ramsay Professor of Chemistry. His research interests span organic and organometallic stereochemistry, asymmetric catalysis, reaction mechanisms, synthesis of functional molecules, and organocatalysis.

chlorosilanes **2** (Scheme 1) have become a testing ground for new chiral nucleophilic catalysts. In general, the reactions display good diastereocontrol in the case of *trans*- and *cis*-crotylsilanes (**2b/2c**), indicating that they are likely to proceed via closed transition states (TSs) **A**. Here, the *anti* diastereoisomer **3b** is obtained from the *trans*-crotyl derivative **2b**, whereas the *syn* isomer **3c** results from the reaction with the *cis* isomer **2c** (Scheme 1). The most successful chiral *N*-oxides are shown in Figure 1.

Nakajima first demonstrated that the axially chiral biquinoline bis-*N*-oxide **4** can catalyze the allylation (Scheme 1) with high yield and enantioselectivity (cat. 10 mol-%, –78 °C, CH_2Cl_2, 71–92% *ee*).[5] His efforts were later followed by those of Hayashi, who reported a similar level of asymmetric induction attained with the bipyridine analogue **5** and its congeners (with 56–98% *ee*).[6] The latter catalyst is remarkable for the loading required for the reaction to occur: it works at the 0.1 mol-% level (–40 °C, MeCN) and retains moderate activity even at 0.01 mol-% loading,[6] which makes this organocatalyst the most reactive one reported to date. A chelation model in which both oxygens of the catalyst coordinate with Si in the reagent has been proposed to account for the reactivity.[6]

Prior to Hayashi's report,[6] Malkov and Kočovský[7] had shown the terpene-derived bipyridine *N*-monoxides PINDOX, Me_2PINDOX, and *iso*-PINDOX **6**–**8** (cat. 10 mol-%, –78 °C, CH_2Cl_2) to be even more enantioselective than the dioxide **4**, although the reaction rate was reduced, especially with the severely hindered *iso*-PINDOX (**8**). The most successful derivative of this series, Me_2PINDOX (**7**), combines the effects of both central and axial chirality, since the rotation about the bond connecting the two pyridine moieties is restricted by the two methyls and the N–O group. However, the barrier to rotation is rather low, and **7** isomerizes within two weeks to a 1:2 mixture of **7** and its atropoisomer, which weakens the asymmetric induction.[7b] PINDOX (**6**) and *iso*-PINDOX (**8**) lack the restriction to the rotation, so a suitable configuration is apparently established on coordination to the silicon atom in the allylating reagent.[7] In analogy to the chelation model proposed for



Scheme 1. Asymmetric allylation of aldehydes.

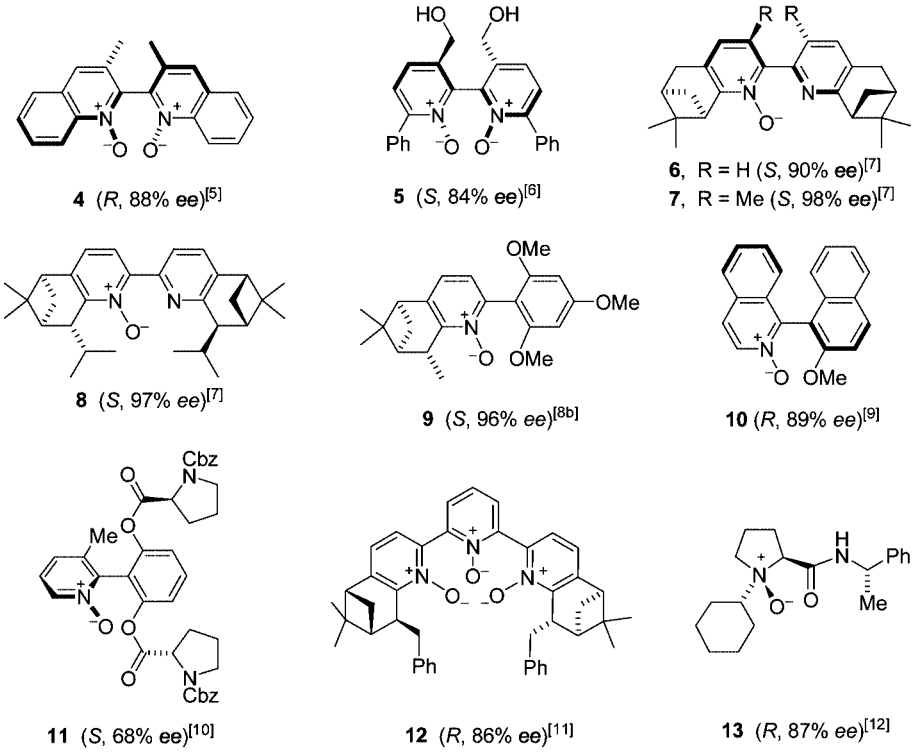


Figure 1. Selected *N*-oxides for allylation reactions and the enantioselectivities attained for the reaction of PhCHO (**1**) with **2a**. The absolute configuration of the product **3a** is shown in parentheses.

4 and **5**, chelation of the silicon in $AllylSiCl_3$ by O and N was considered for **6**–**8**.[7] However, METHOX (**9**), lacking the second pyridine ring, turned out to be much more reactive than **6**–**8** with the same level of enantioselectivity being attained (≤96% *ee* at 1–5 mol-% loading, –40 °C, MeCN),[8] suggesting that coordination to nitrogen in **6**–**8** may not play an important role. Instead, arene-arene interactions between the catalyst and the substrate have been suggested to account for the high reactivity and selectivity. Furthermore, the case of METHOX (**9**) shows clearly that the axial chirality, whether predetermined (as in **4** and **5**) or induced during the reaction (**6** and **8**), is not an absolute prerequisite for attaining high enantioselectivity in the allylation reaction.[8]

Another two pyridine-type mono-*N*-oxides, namely **10** (QUINOX)[9] and **11**,[10] have also been reported as successful organocatalysts, and the series is complemented by the *N*,*N*′,*N*′′-trioxide **12**[11] and the chiral-at-nitrogen *N*-oxide **13**,[12] the only representative of aliphatic tertiary amine *N*-oxides so far reported in this series. It is pertinent to note that catalysts **9**[8b] and **13**[12] retain high enantioselectivity even at room temperature.

A number of other pyridine *N*-oxide catalysts incorporating a binaphthyl unit[13] or helically chiral polymethacrylates[14] in their designs have been reported, but the selectivities of the allylations they have catalyzed have been low.

Crotylation catalyzed by the *N*-oxides **4**–**9**[5–9] is highly diastereoselective, with the *trans* isomer **2b** affording the *anti* product **3b** almost exclusively, while the *cis* isomer **2c** gives mostly the *syn* product **3c** (although in a slightly slower reaction). This behavior is consistent with the cyclic chair-like transition state **A** (Scheme 1), which guarantees a high degree of stereocontrol. METHOX (**9**) represents an extreme case, as it reacts well only with **2b**, affording **3b** with excellent diastereocontrol (>99:1) and enantioselectivity (95% *ee*), while the reaction with **2c** is very slow and less diastereoselective (6:1).[8b] In contrast, QUINOX (**10**) has been shown to exhibit rather low diastereocontrol,[9] which may indicate the participation of either a cyclic boat-like or an open transition state. Furthermore, it is important to note that the catalytic efficiency of QUINOX (**10**) proved to be very sensitive to the substitution pattern, particularly in the position next to the *N*-oxide group. Analogues **14**,[15] **15**,[16] and **16**[17] (Figure 2) thus exhibited dramatically reduced reactivities and enantioselectivities (in relation to **10**) in allylation of benzaldehyde with **2a** (ca. 20% *ee*). The mechanism of catalysis by QUINOX is currently under investigation.[15]

The effect of the electronic properties of the substituted benzaldehydes **1a**–**c** on the allylation reaction is another interesting issue. While the majority of the catalysts shown in Figure 1 generally exhibit rather minor variation in the *ee* (typically with less than 20% difference between electron-rich and electron-poor aldehydes), METHOX (**9**) appears to be a particularly tolerant catalyst, exhibiting practically the same enantioselectivity (93–96% *ee*) and reaction rate across the range of substrates.[8b] In contrast, QUINOX (**10**) lies at the other end of the spectrum, showing the most

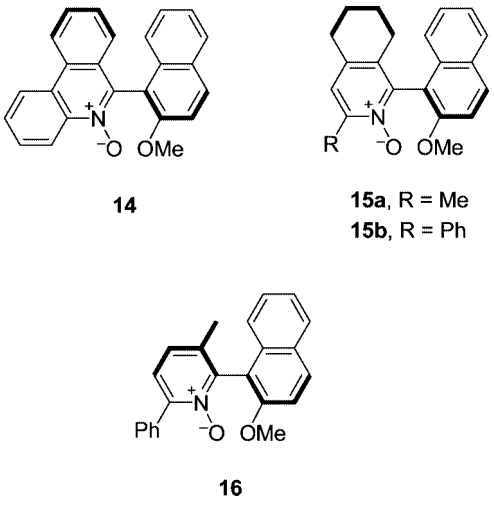
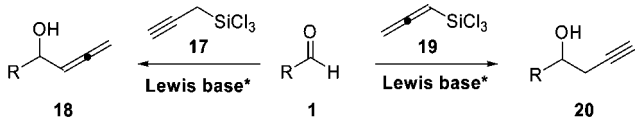


Figure 2. Analogues of QUINOX (**10**).

dramatic differences between the electron-poor and electron-rich substrate aldehydes (*p*-$CF_3C_6H_4CHO$ provides a 96% *ee*, whereas *p*-$MeOC_6H_4CHO$ gives a mere 12% *ee*).[9]

2.2. Propargylation and Allenylation of Aldehydes

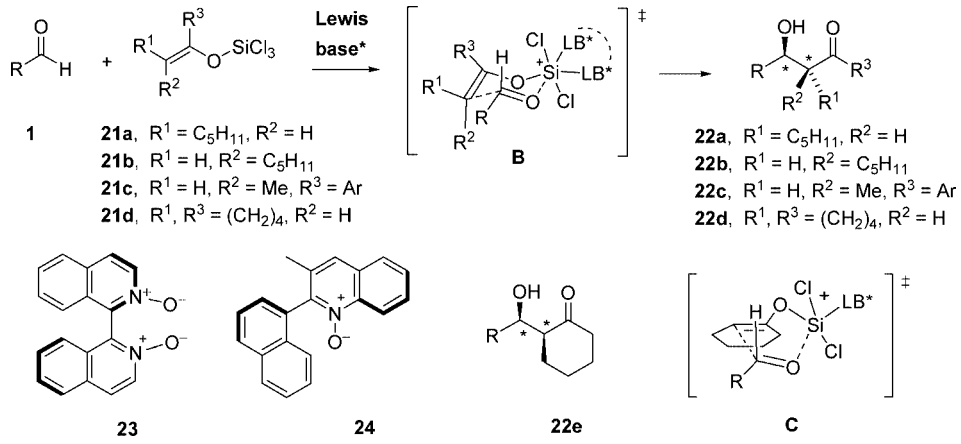
Reactions between propargyl trichlorosilane (**17**) and aromatic, heteroaromatic, and cinnamyl-type aldehydes **1**, mediated by DMF (acting as a Lewis base), have been shown to occur analogously to allylation, producing allenyl alcohols **18** with >99:1 selectivity (Scheme 2). Similarly, allenyl trichlorosilane (**19**) gives homopropargyl alcohols **20**.[18,19] The reagents **17** and **19** were synthesized by metal-catalyzed reactions between propargyl chloride and Cl_3SiH: CuCl catalysis gave **17** (>99:1), whereas the reaction catalyzed by $(acac)_2Ni$ produced **19** (>99:1).[18,19] The asymmetric version has been reported by Nakajima,[19a] who employed the axially chiral biquinoline bis-*N*-oxide **4** as catalyst (10 mol-%) but the enantioselectivities attained were rather modest (40–62% *ee*). It is noteworthy that, unlike with other propargylic and allenic organometallics, no metallotropic interconversion of **17** and **19** has been observed, which points to an interesting potential of this methodology.[18,19]



Scheme 2. Propargylation and allenylation of aldehydes.

2.3. Asymmetric Aldol Reactions

Aldol additions of trichlorosilyl enol ethers to aldehydes proceed readily at room temperature without a catalyst. The reaction exhibits simple first-order kinetics in each component,[20] reflecting the higher nucleophilicity of silyl enol ethers relative to the corresponding allylsilanes.[21] Never-

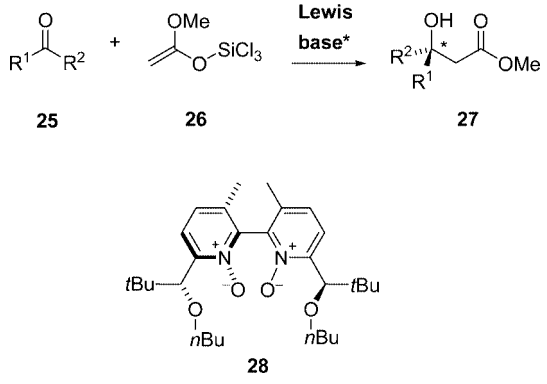


Scheme 3. Asymmetric aldol additions of trichlorosilyl enol ethers to aldehydes.

theless, the reaction is substantially accelerated by Lewis bases, which provided solid grounds for the development of an asymmetric variant. Denmark introduced a range of efficient chiral phosphoramides as nucleophilic activators for enantioselective C–C bond formation and also carried out a detailed mechanistic investigation.[20,22,23] Bidentate and smaller monodentate catalysts were shown to react through a cationic chair-like transition state **B** with octahedral extracoordinate silicon (Scheme 3). According to this scheme, (*Z*)-enol ethers **21b** and **21c** produced *syn* adducts **22b** and **22c**, whereas (*E*) derivatives **21a** and **21d** furnished *anti* diastereoisomers **22a** and **22d**. In the case of a bulky monodentate activator, in which coordination of the second catalyst molecule is precluded by steric factors, the diastereoselectivity of the reaction was reversed. Here, the reaction presumably proceeds via the cationic boat-like TS **C**, in which the silicon is pentacoordinate. According to this scheme, the cyclohexanone-derived enol ether **21d** with a fixed (*E*) configuration of the double bond gave rise to the *syn* product **22e**.[20,23]

The true potential of chiral *N*-oxides to promote aldol additions still remains to be explored, since only a few examples have been reported.[24] Catalysis by *N*-oxides follows the same general trends as established for the phosphoramide activators, though with reduced enantioselectivity. Thus, Nakajima[24] has demonstrated that the reactions between aldehydes **1** and silyl enol ethers **21**, catalyzed by bidentate bis-*N*-oxides **4** and **23** [catalyst 3 mol-%, 1 equiv. of (*i*Pr$_2$)NEt, CH_2Cl_2, –78 °C], proceed via TS **B**, resulting in high diastereoselectivity and moderate to good enantioselectivity (up to 82% *ee*). On the other hand, aldol reactions between cyclic silyl enol ethers of type **21d** and aromatic aldehydes, catalyzed by bulky mono-oxides **10** and **24**, displayed *syn* selectivity, consistently with involvement of the TS **C**. The enantioselectivity remained modest in the latter case (up to 72% *ee*).[24]

Generally, the range of substrates both in allylations and in aldol condensations employing trichlorosilyl reagents is restricted to more reactive aldehydes, while ketones remain essentially inert. However, the exceptionally high nucleophilicity of silyl ketene acetals[21] offers an opportunity to use ketones as substrates. In the absence of an activator, addition of trichlorosilyl ketene acetal **26** to acetophenone (**25**, R^1 = Ph, R^2 = Me, Scheme 4) slowly takes place at 0 °C, paving the way for the development of a catalytic asymmetric variant. Among a large number of Lewis basic promoters investigated, bis-*N*-oxides have emerged as the most promising class in terms of reactivity and enantioselectivity (cat. 10 mol-%, –20 °C, CH_2Cl_2).[25] A new procedure for the synthesis of atropoisomeric bis-*N*-oxides has been developed,[26] with the bis-*N*-oxide (S_{ax},*R*,*R*)-**28**, with a matched combination of axial and central chirality, delivering the best results (up to 86% *ee*), while the mismatched counterpart furnished the opposite enantiomers of **27** with substantially reduced selectivities. Catalysts **4** and **23** also proved inferior.[25]



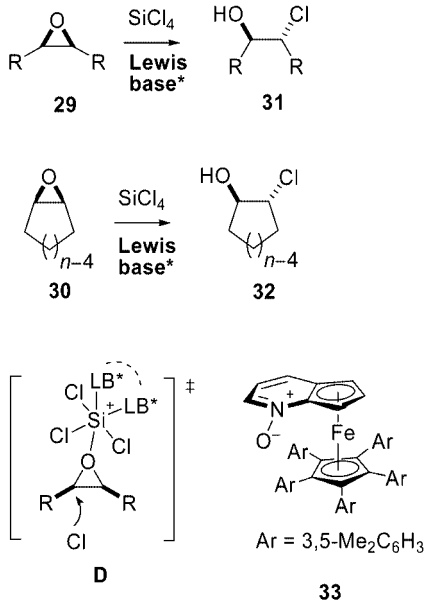
Scheme 4. Asymmetric aldol addition of trichlorosilyl ketene acetals to ketones.

2.4. Asymmetric Opening of *meso*-Epoxides

Epoxides are among the most versatile intermediates in organic synthesis, thanks to their potential for controlled stereoselective ring-opening. In the case of *meso*-epoxides, addition of nucleophiles allows two adjacent stereogenic centers to be installed simultaneously.

The abilities of various chlorosilanes to serve as sources of chloride for epoxide-opening were reported almost half

a century ago,[27] and it was later demonstrated that the reaction can be dramatically accelerated in the presence of nucleophilic catalysts (Scheme 5).[28] The mechanism of the Lewis base assisted opening of epoxides with tetrachlorosilane has not been established in detail, but it can be suggested that the reaction takes place via TS **D**, in which the epoxide is coordinated through the oxygen atom to the silicon species, the Lewis acidity of which is enhanced by extracoordination.[3] Opening of the activated epoxide by chloride ion then proceeds, as expected, in an S_N2 fashion.



Scheme 5. Asymmetric opening of *meso*-epoxides.

In general, the efficiencies of the catalysts have been found to be substrate-dependent; none of the known catalysts was able to provide a good level of enantioselectivity with a wide range of acyclic (**29**) and cyclic (**30**) epoxides. The planar chiral pyridine *N*-oxide **33**, developed by Fu,[29] exhibited high enantioselectivity in the opening of *cis*-stilbene oxide derivatives **29** (R = Ar, cat. 5 mol-%, –85 °C, CH_2Cl_2, *ee* 91–98%). Similarly, axially chiral bis-isoquinoline *N*,*N*′-dioxide **23** (cat. 10 mol-%, –78 °C, CH_2Cl_2) displayed high efficiency, furnishing chlorohydrin **31** (R = Ph) in 90% *ee*.[30] In the case of less sterically demanding aliphatic (**29**, R = CH_2OBn) and cyclic (**30**, *n* = 5–7) substrates, the selectivities of these catalysts dropped to moderate levels. Cyclooctene oxide (**30**, *n* = 8) proved to be a particularly difficult substrate, showing low reactivity and selectivity with most of the catalysts, except for PINDOX (**6**), which produced the corresponding chlorohydrin **32** (*n* = 8) in 85% *ee*,[7a] although this catalyst was considerably less efficient with other substrate types.

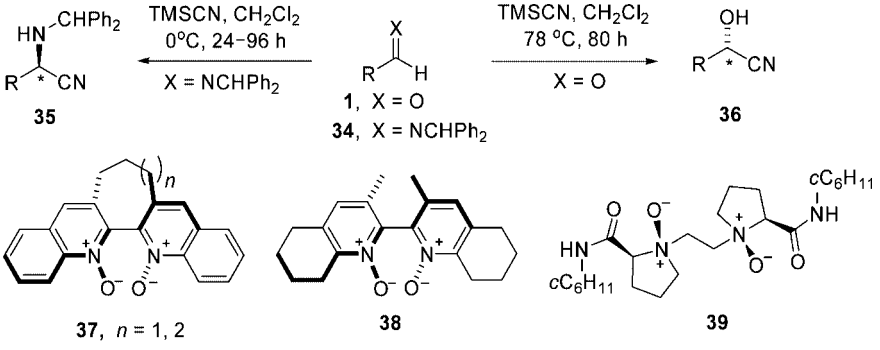
2.5. Cyanosilylation of Aldehydes and Aldimines

The synthetic value of the addition of cyanide to aldehydes and imines stems from the fact that it provides easy access to a vast variety of α-hydroxy and α-amino acids.[31]

Asymmetric Strecker reactions mediated by chiral *N*-oxides were investigated by Feng;[32] along with bisoxides **4** and **23**, a number of other analogues such as **37** and **38** (Scheme 6) were tested. Compounds **37** were synthesized in racemic form and were then resolved into enantiomers by use of L- or D-dibenzoyltartaric acid. Catalyst **38** was obtained by the Pt-catalyzed hydrogenation of enantiopure **4**.

In the cyanation of benzhydrylimines **34**, the best results were obtained with bis-*N*-oxide **4**. For the optimal performance, the promoter had to be used in stoichiometric quantities, since reduced loadings resulted in lower selectivity. Under optimized reaction conditions (1 equiv. of **4**, 0 °C, CH_2Cl_2), a wide range of aromatic substrates were converted into the corresponding α-aminonitriles **35** in high yields and with moderate to good enantioselectivity. Electron-poor substrates displayed better reactivity and selectivity than their electron-rich counterparts, whilst in many cases the enantiopurities of the products could be brought to 99% through recrystallization.

In a related cyanosilylation of aldehydes (**1**→**36**, Scheme 6), Feng[33] developed a new bis-*N*-oxide **39**, derived from proline, as a rare example of a non-pyridine system. Cyanation of aldehydes can be carried out by using catalytic quantities of the activator **39** (2.5 mol-%), comparing favorably with the analogous addition to imines, in which the promoter has to be used in stoichiometric amounts. Under optimized conditions (–78 °C, CH_2Cl_2, 80 h) a wide range of cyanohydrins **36** were obtained in good yields and with enantioselectivities of up to 73%.[33]



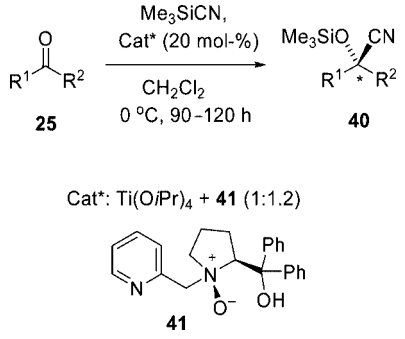
Scheme 6. Asymmetric cyanation of aldehydes and aldimines.

3. Metal-Catalyzed Reactions

Amine *N*-oxides have been recognized as efficient ligands for transition metal complexes.[34] Furthermore, pyridine *N*-oxides can be viewed as neutral structural analogues of the widely popular anionic phenolate systems.[35] However, development in this area still has not reached the desired level of efficiency, and application of *N*-oxides in metal-mediated asymmetric synthesis remains limited to a few successful attempts.

3.1. Cyanosilylaton of Ketones

The use of Lewis acidic transition metal complexes opens an opportunity to employ the less electrophilic ketones **25** as substrates for cyanation, thus creating quaternary stereogenic centers such as in **40** (Scheme 7). Feng has developed bifunctional catalytic systems based on complexes of $Ti(OiPr)_4$ with chiral *N*-oxides, such as **41**.[36] Coordination of titanium through the pyridine nitrogen and the tertiary hydroxy group was suggested, while the *N*-oxide moiety is believed to provide nucleophilic assistance for ionization of TMSCN. A number of aromatic ketones were converted into the corresponding cyanohydrins **40** in good yields but the enantioselectivities were only modest (up to 69% *ee*).[36]



Scheme 7. Asymmetric cyanosilylation of ketones.

3.2. Michael Additions

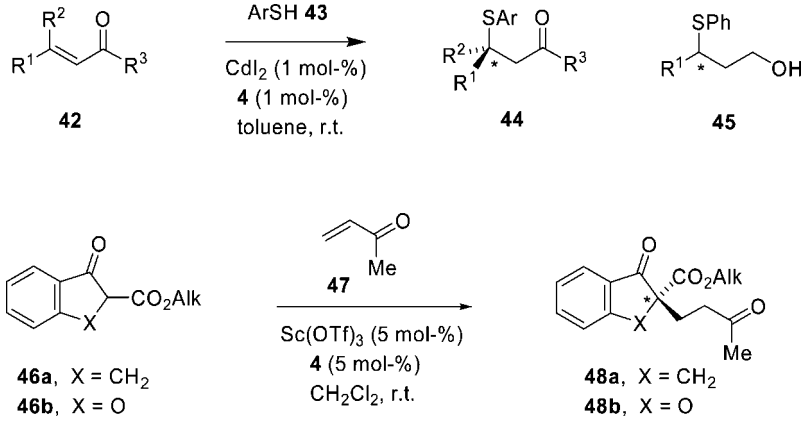
The catalytic utility of the axially chiral 2,2′-biquinoline *N*,*N*′-dioxide **4** as an efficient activator of organosilicon reagents has been extended to metal-based systems. Nakajima developed a procedure in which a complex of CdI_2 with **4** was employed to catalyze enantioselective conjugate additions of thiophenols **43** to α,β-unsaturated carbonyl compounds **42** (Scheme 8).[37] Cyclic enones and acyclic unsaturated aldehydes reacted well, whereas acyclic unsaturated ketones such as chalcone proved unreactive. The resulting sulfides **44** were obtained in high yields and with enantioselectivities of up to 78%. For characterization, the aldehyde adducts (R^3 = H) were converted into alcohols **45** by reduction with $NaBH_4$ in methanol. Mechanistic investigation revealed a slight positive nonlinear effect, suggesting some degree of aggregation of the active catalyst, though no further details were revealed.[37b]

In a related process, a complex of *N*,*N*′-dioxide **4** with $Sc(OTf)_3$ was found to catalyze enantioselective Michael additions of β-keto esters **46** to methyl vinyl ketone (**47**) effectively (Scheme 8), with *ee* values of up to 80%. The reaction was also extended to acrolein as the Michael acceptor, which furnished the corresponding product **48** in 75% *ee*.[38]

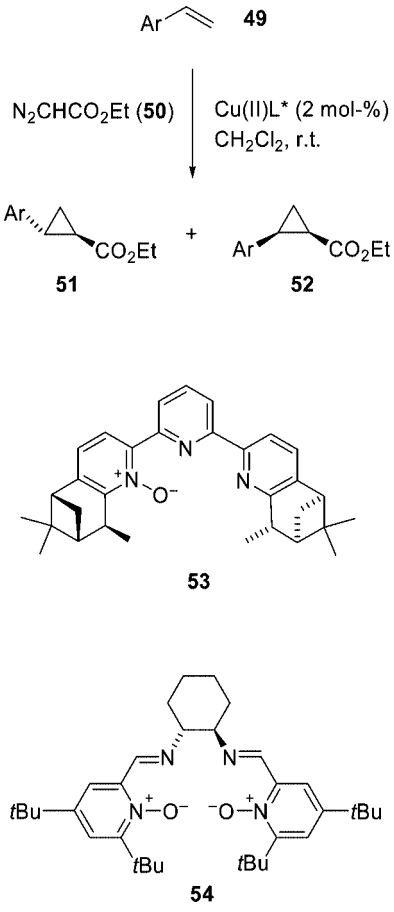
3.3. Miscellaneous Reactions

Kwong[39] screened a number of terpyridines derived from the natural terpene pool and their corresponding mono- and di-*N*-oxides as ligands for Cu^I-catalyzed asymmetric cyclopropanation of styrenes **49** with ethyl diazoacetate (**50**). The mono-*N*-oxide **53** (Scheme 9), along with the parent terpyridine, emerged as the best ligands, giving a mixture of *trans*-**51** and *cis*-**52** in a 66:34 ratio and with 73% and 83% *ee* values, respectively. In spite of the similar diastereo- and enantioselectivities, the active species in the case of the terpyridine and its mono-*N*-oxide **53** are likely to be different, as evidenced by Hammett correlation studies.[39]

Dyker[40] introduced the bis-*N*-oxide **54**, an isoelectronic neutral analogue of Jacobsen's salen ligand.[41] A number of complexes of **54** with metals in low oxidation states were synthesized and the Cu^I complex was tested in asymmetric cyclopropanation (Scheme 9), but the observed diastereoselectivities and enantioselectivities were poor (for styrene



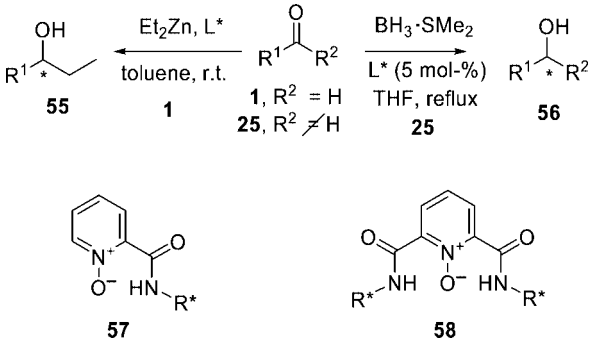
Scheme 8. Asymmetric Michael additions.



Scheme 9. Asymmetric cyclopropanation.

the *cis*/*trans* ratio was 45:55 and the enantiomeric excesses were 21% and 15%, respectively).[40]

Pyridine *N*-oxides **57** and **58** were synthesized from the corresponding 2-picolinic and pyridine-2,6-dicarboxylic acids, respectively, by a sequence of transformations involving oxidation with H_2O_2/AcOH, followed by coupling with a number of natural amino acids and norephedrine. The compounds were employed as catalysts in the addition of Et_2Zn to aldehydes (**1**→**55**, Scheme 10) and in the reduction of prochiral ketones with borane (**25**→**56**), but no useful selectivities were observed.[42]



Scheme 10. Asymmetric reduction of ketones and alkylation of aldehydes.

Finally, brucine *N*-oxide has been reported to facilitate asymmetric Pauson–Khand reactions with *ee* values of up to 78%,[43] although this process is currently stoichiometric and its catalytic version still remains to be developed.

4. Conclusions

In this microreview we have highlighted the utilization of amine *N*-oxides in asymmetric catalysis. The most popular derivatives in this class are those with a pyridine (or quinoline-type) scaffold, and the most successful catalysts of this type were designed for the activation of silicon reagents, in particular allylsilanes **2a**–**c** and silyl enol ethers **21a**–**d** and **26** for allylations of aldehydes and aldol condensations, respectively. The champion catalysts in these reactions are **5**, **9**, and **28**, all characterized by high reactivity and enantioselectivity (≤99% *ee*). The *N*-oxides are also capable of coordinating metals, but catalysts based on this class of ligands have not yet reached useful levels of efficiency.

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