The development and application of chiral trisoxazolines in asymmetric catalysis and molecular recognition

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The development of suitable ligands that upon coordination to a metal facilitate enantioselective reactions or are able to selectively recognize a molecule are fundamental endeavours in organic chemistry. Chiral ligands that contain one or two oxazoline groups have been extensively studied and applied successfully to many metal catalyzed reactions. Accordingly, the development and application of chiral trisoxazolines has received increasing attention in the last decade. This tutorial review covers the synthetic methods for the preparation of chiral trisoxazolines, the application of chiral trisoxazolines in asymmetric catalysis and molecular recognition.

Introduction

During the past decade there has been a rapid growth in the development and application of bisoxazolines.[1–3] A number of bisoxazolines, derived from different linkages, backbones and amino alcohols, have already been applied to a series of metal catalyzed C–C bond forming reactions such as aldol, Diels–Alder, hetereo-Diels–Alder, Friedel–Crafts, Michael addition, Mannich, cycloadditon, arizidination, free radical, amination and halogenation reactions.[1–4] Besides the intrinsic advantages of oxazoline ligands, such as easy accessibility, modular nature, stability towards hydrolysis and oxidation, and facile coordination to a wide range of transition metals, an important advantage of oxazoline ligands is that the stereogenic centres neighbouring the coordinating nitrogen atom of the oxazoline ring, are held in close proximity to the metal thus exerting a strong and direct influence on the stereochemical outcome of metal catalyzed processes.[5]

Inspired by the versatility of bisoxazolines, the synthesis and application of trisoxazolines (TOX) receive increasing attention, with the anticipation that trisoxazolines could have some important characteristic differences from bisoxazolines: 1) The third oxazoline in a trisoxazoline is expected to increase the stability of a metal complex,[6] so that a chiral catalyst might be air- and water- tolerant. Accordingly, it should be possible to carry out the reactions in mild conditions, exposed to air for example; 2) trisoxazolines create a more sterically encumbered chiral space than bisoxazolines, which might reduce disadvantages such as rotation and flexibility in enantiofacial control, therefore it is then also possible to employ cheap chiral sources with small steric biases to achieve excellent enantioselectivity; 3) As far as symmetry is concerned, it is generally believed that bidentate C_2-symmetry reduces the number of possible diastereomers in catalytic intermediates for square planar

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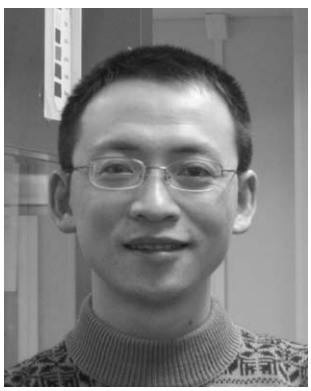

Zhou Jian

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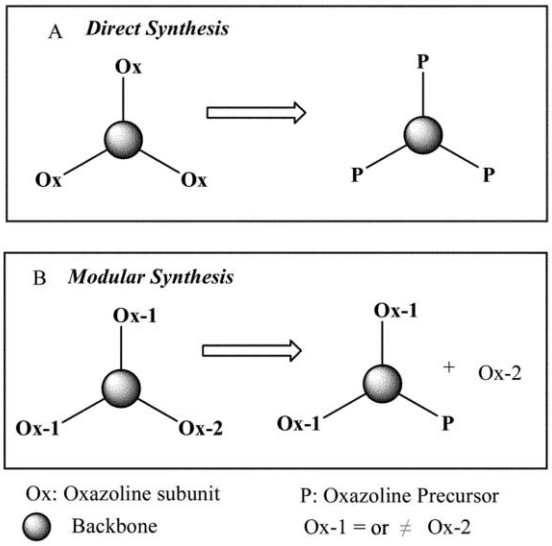
geometries, while C_3-symmetry can do the same for octahedral intermediates. In this light, C_3-symmetric trisoxazolines might be versatile in metal catalysed asymmetric reactions involving octahedral intermediates.[7] In addition, trisoxazolines can also be synthesized in a direct or modular way, which can greatly improves the ligand diversity[8] and provides access to ligands capable of achieving excellent selectivity for a wide range of asymmetric reactions.

Trisoxazolines first emerged in 1993, when Sorrell and co-workers reported the synthesis of achiral trisoxazoline **3**.[9] It was in 1995 that the synthesis and application of a chiral analogue trisoxazoline **3** in an asymmetric Kharash–Sosnavsky reaction was accomplished by Katsuki *et al*.[10] Since then, several types of trisoxazolines, including C_3-symmetric and pseduo-C_3-symmetric, homochiral and heterochiral†, have been developed, and these ligands have already found utility in asymmetric catalysis and molecular recognition. In several asymmetric reactions, trisoxazolines have shown substantial improvement in enantiofacial selectivity compared to the relative bisoxazolines. Furthermore, in the area of molecular recognition, C_3-symmetric trisoxazolines also proved to have some unique features as artificial receptors. Although trisoxazolines have shown promising properties both in asymmetric catalysis and in molecular recognition, there lacks a comprehensive summary of work associated with trisoxazolines, casting light on the further development of superior trisoxazolines. To date, they are only partially mentioned in a recent review dealing with oxazoline-containing ligands.[4] In this light, here we sum up the synthetic strategies and methods for the preparation of trisoxazolines and their application in asymmetric catalysis and molecular recognition. Limitations and anticipations are also discussed in this article.

Synthesis of trisoxazolines

There have been two strategies developed for the synthesis of trisoxazolines (Scheme 1). One is to directly construct three oxazolines in one step. The advantage of this method is that it enables the synthesis of the ligands in relatively few steps and thus this strategy is mostly adopted. However, direct synthesis sometimes suffers from poor yields in the key step and, in addition, this method can only be used to prepare homochiral trisoxazolines with the same oxazoline subunit (A, Scheme 1); The other method is to construct three oxazolines in a modular manner (B, Scheme 1). In this strategy, a building block with a bisoxazoline framework is first synthesized. This contains an oxazoline precursor that can be directly transformed to the third oxazoline, or can be coupled with another preformed oxazoline unit to complete the synthesis of the trisoxazolines. Although indirect, the most promising characteristic of this modular method is that it enables the synthesis of trisoxazolines with different oxazoline subunits, so that both homochiral and heterochiral trisoxazolines can be synthesized at will, which is of great benefit in the construction of a diverse trisoxazoline ligand library.

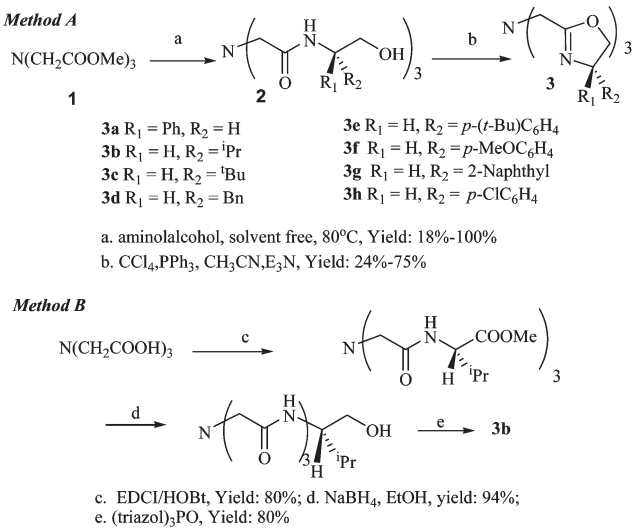
† Homochiral trisoxazolines referred to trisoxazolines with three oxazoline subunits same, while in hetero trisoxazolines, the oxazoline subunits are different from each other (or at least one oxazoline subunit is different from the other two).



Scheme 1

Direct synthesis. Whether using the direct or modular synthetic approach for trisoxazolines, chiral oxazolines are usually prepared by coupling of a carboxylic acid or its derivatives with amino alcohols followed by ring formation or by direct condensation of nitriles with amino alcohols in the presence of a Lewis acid such as $ZnCl_2$.[1] Most recently, a novel oxazoline exchange reaction with amino alcohols was also introduced for the synthesis of trisoxazolines.[11]

The first chiral trisoxazoline **3** derived from nitrilotriacetate **1** was developed by Katsuki's group, using a direct strategy to construct three oxazolines in concert.[10,12] Nitrilotriacetate **1** reacted with different amino alcohols smoothly under a solvent-free condition. By treating with PPh_3/CCl_4, triamides **2** underwent cyclization in moderate to good yields (Method A, Scheme 2). Chang *et al* reported a different synthetic route for trisoxazoline **3b** (Method B).[13] Obviously, only homochiral trisoxazolines could be obtained by the two methods.



Scheme 2

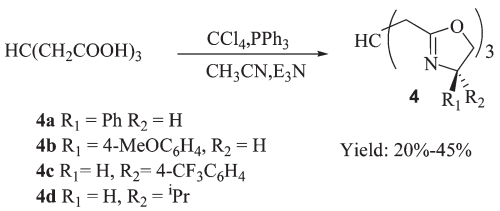
Another type of C_3-symmetric trisoxazoline **4**, similar to trisoxazoline **3** but with a carbon atom as the core, was also developed by Katsuki's group in 2000.[14] Trisoxazoline **4** was designed to test if the core nitrogen atom of trisoxazoline **3** would coordinate to the metal centre and influence the structure of the catalytic species and affect the enantioselectivity. The synthesis of trisoxazoline **4** was accomplished in only one step from methanetriacetic acid and chiral amino alcohols (Scheme 3), using PPh_3, CCl_4/Et_3N to facilitate the ring closure.

Also in this year, C_3-symmetric trisoxazolines **5**, with a rigid cyclohexane backbone, was prepared from Kemp's triacid by Fang and Bolm.[15] In this direct synthesis, triester reacted with amino alcohols in the presence of NaH to afford the desired triamides in low to moderate yields, which were treated with PPh_3/CCl_4 or Et_2NSF_3 to provide trisoxazoline **5** (Scheme 4).

A benzene-based C_3-symmetric trisoxazoline **6** was reported by Ahn in 2000 (Scheme 5).[16] The synthetic methods were as follows: Transformation of benzene tricarboxylic acids to the corresponding triacid chlorides, followed by reaction with amino alcohols afforded the triamides in good yields. Ring closure was completed by treatment of the amides with $SOCl_2$, and then refluxing in methanolic NaOH solution.

A similar benzene-based C_3-symmetrical trisoxazoline **7** was independently synthesized by Hong *et al.* the following year. The synthetic methods were by and large the same as those of trisoxazoline **6** (Scheme 6).[17]

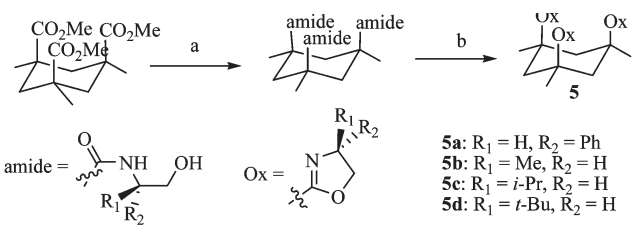
Although most attention was paid to the development of symmetric trisoxazolines, our group tried a pseudo-C_3-symmetric trisoxazoline construct **8**. With an additional carbon on the linker, the third oxazoline was regarded as a side-arm to a classical bisoxazoline. Trisoxazoline **8** could be synthesized in moderate to good overall yield using a similar strategy for the preparation of trisoxazoline **3**.[18] Another type of pseudo-C_3-symmetric trisoxazoline **9**,[19] with two more carbon atoms on the bridge, was also prepared in the same manner.



4a R_1 = Ph R_2 = H
4b R_1 = 4-$MeOC_6H_4$, R_2 = H
4c R_1= H, R_2= 4-$CF_3C_6H_4$
4d R_1 = H, R_2 = ^{i}Pr

Yield: 20%-45%

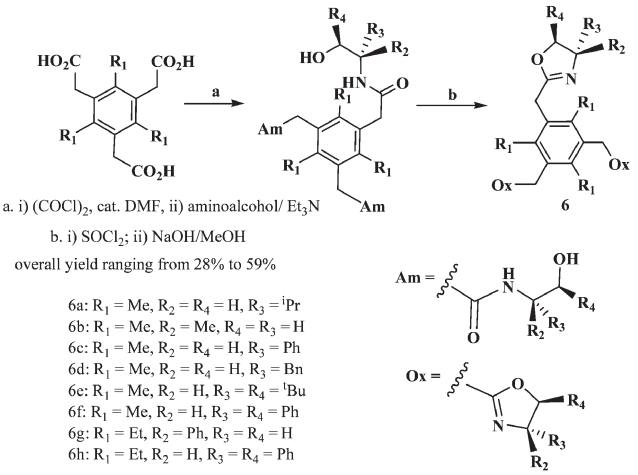
Scheme 3



5a: R_1 = H, R_2 = Ph
5b: R_1 = Me, R_2 = H
5c: R_1 = *i*-Pr, R_2 = H
5d: R_1 = *t*-Bu, R_2 = H

a. NaH/toluene, aminoalcohol, Yield: 18-54%
b. PPh_3, CCl_4, Et_3N, CH_3CN,Yield: 50-81%

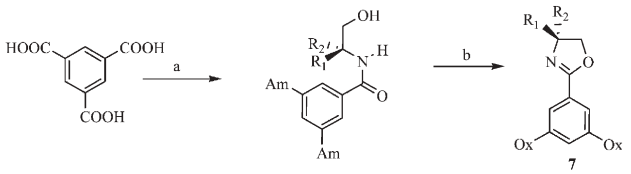
Scheme 4



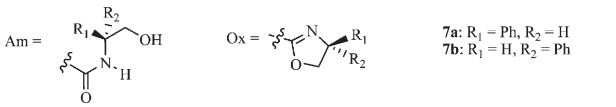
a. i) $(COCl)_2$, cat. DMF, ii) aminoalcohol/ Et_3N
b. i) $SOCl_2$; ii) NaOH/MeOH
overall yield ranging from 28% to 59%

6a: R_1 = Me, R_2 = R_4 = H, R_3 = ^{i}Pr
6b: R_1 = Me, R_2 = Me, R_4 = R_3 = H
6c: R_1 = Me, R_2 = R_4 = H, R_3 = Ph
6d: R_1 = Me, R_2 = R_4 = H, R_3 = Bn
6e: R_1 = Me, R_2 = H, R_3 = R_4 = ^{t}Bu
6f: R_1 = Me, R_2 = H, R_3 = R_4 = Ph
6g: R_1 = Et, R_2 = Ph, R_3 = R_4 = H
6h: R_1 = Et, R_2 = H, R_3 = R_4 = Ph

Scheme 5



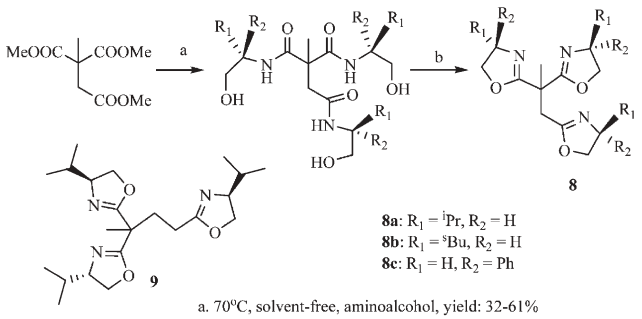
a. i) $(COCl)_2$, cat. DMF; ii) aminoalcohol, Et_3N b. i) MsCl (3 eq.), TEA (6 eq) 95% yield



7a: R_1 = Ph, R_2 = H
7b: R_1 = H, R_2 = Ph

Scheme 6

Modular synthesis. As aforementioned, although a direct synthesis could conveniently afford the desired homochiral trisoxazolines in relatively few steps, it failed to provide heterochiral trisoxazolines, a limitation of the strategy itself. In this light, modular synthesis emerged as a promising strategy to expand the diversity of trisoxazolines. From the point of view of ligand design, the possibility of introducing and combining different substituents at the oxazoline rings, chiral or achiral units, even oxazoline ligands with opposite absolute



8a: R_1 = ^{i}Pr, R_2 = H
8b: R_1 = ^{s}Bu, R_2 = H
8c: R_1 = H, R_2 = Ph

a. 70°C, solvent-free, aminoalcohol, yield: 32-61%
b. PPh_3, CCl_4/CH_3CN, Et_3N, yield: 68-75%

Scheme 7

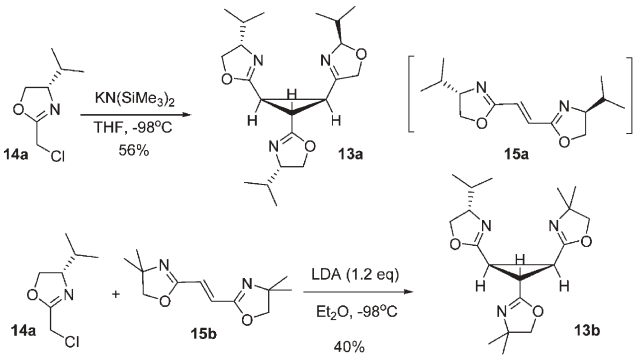
configuration within the same tripodal ligand system allowed a straightforward access to a large variety of such systems.

Gade *et al.* first introduced a modular strategy for the synthesis of a chiral trisoxazoline when preparing **12**.[20] The purpose of this method was initially employed to overcome the decarboxylation and decomposition of the precursors during the formation of the oxazoline ring associated with direct synthesis. It turned out that modular synthesis was a versatile method for obtaining homochiral as well as heterochiral trisoxazolines. The coupling of bisoxazoline **10** with 2-bromooxazoline **11** afforded different kinds of trisoxazolines (both homochiral and heterochiral) in good to excellent yields (Scheme 8).

Florio *et al.* also developed a novel chiral trisoxazoline **13** in a modular fashion.[21] The treatment of (4*S*)-2-chloromethyl-4-isopropyl-2-oxazoline **14a** with $KN(SiMe_3)_2$ in THF at low temperature produced the *trans*-tris(oxazolinyl)cyclopropane **13a** (one predominant stereoisomer) (Scheme 9), probably *via* a 1,4-addition of the metallated 2-chloromethyl-2-oxazoline **14a** to the corresponding alkene intermediate **15a** generated *in situ*. Based on this hypothesis, the authors also developed a trisoxazoline **13b** with different oxazolinyl appendages *via* Michael addition of 2-chloromethyl-2-oxazoline **14a** to the *trans*-bis(oxazolinyl)-ethene **15b**.

In the process of synthesizing heterochiral benzene-based trisoxazoline **6**, Ahn *et al.* developed a novel oxazoline exchange reaction with amino alcohols (method B, Scheme 10). With this methodology, modular synthesis of trisoxazoline **6** became more effective than the sequential formation of the third oxazoline *via* the use of a cyano group as the precursor in bisoxazoline **15** (method A). The scope of this method was demonstrated by the successful synthesis of several heterochiral trisoxazolines **6i–m**.[11]

Most recently, our group also successfully expanded the pseudo-C_3-symmetric trisoxazoline **8** based ligand library by

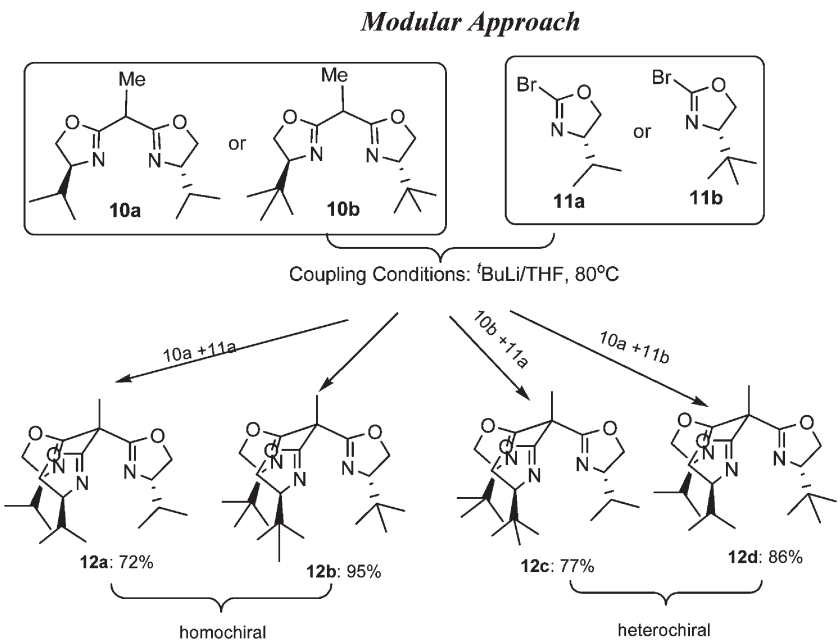


Scheme 9

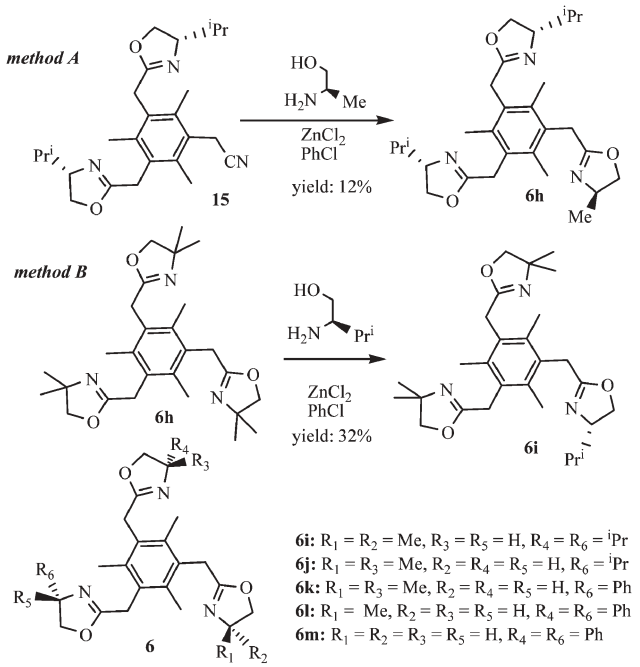
modular synthesis, as shown in Scheme 11. This improvement allowed the incorporation of a broad variety of substituents to the stereogenic centre such as benzyl, *tert*-butyl and indenyl groups to construct homochiral and heterochiral trisoxazolines. It also should be noted that homochiral trisoxazoline **8i** could not be obtained by the previously used direct synthesis, demonstrating the superiority of the modular synthesis.[22]

Trisoxazolines in asymmetric catalysis

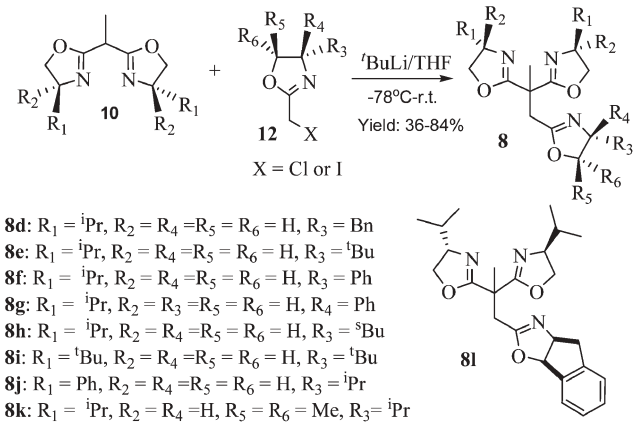
Since compound **3** was first employed in the asymmetric allylic oxidation, trisoxazolines with different structures have already found utility in several asymmetric reactions such as Kharash–Sosnovsky, Friedel–Crafts, Michael addition, Kinugasa, 1,3-dipolar cycloaddition, Diels–Alder reaction, the addition of diethylzinc reagent to aldehyde, cyclopropanation and kinetic resolution of racemic chiral esters by transesterification. Excellent results have been achieved in some of these reactions. Most importantly, trisoxazolines prove to be superior to relative bisoxazolines in some cases, which demonstrates that the catalyst property (both electronic and steric) of



Scheme 8



Scheme 10

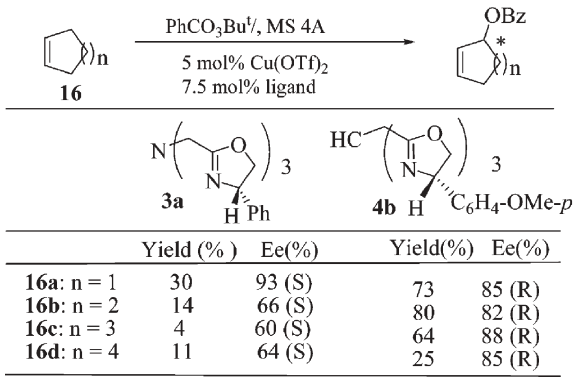


Scheme 11

trisoxazolines indeed differs from that of bisoxazolines. In this review, we arrange the application of trisoxazolines in asymmetric catalysis according to different reaction types and make a comparison between trisoxazolines and bisoxazolines if possible.

Kharash–Sosnovsky reaction. Several types of trisoxazolines had already been employed in this reaction. TOX **3** was the first to be tried. After carefully examining the effect of metal salt, solvent, oxidant, ligand structure and additive, it was found that phenyl-substituted ligand **3a** in combination with $Cu(OTf)_2$ could promote the oxidation of cyclopentene with up to 93% ee in acetone. However, other cycloalkenes only afforded low yield and moderate enantioselectivity (Scheme 12).[10,12]

Considering that the nitrogen atom at the core of trisoxazoline **3a** might coordinate to the copper centre, it was



	Yield (%)	Ee(%)	Yield(%)	Ee(%)
16a: n = 1	30	93 (S)	73	85 (R)
16b: n = 2	14	66 (S)	80	82 (R)
16c: n = 3	4	60 (S)	64	88 (R)
16d: n = 4	11	64 (S)	25	85 (R)

Scheme 12

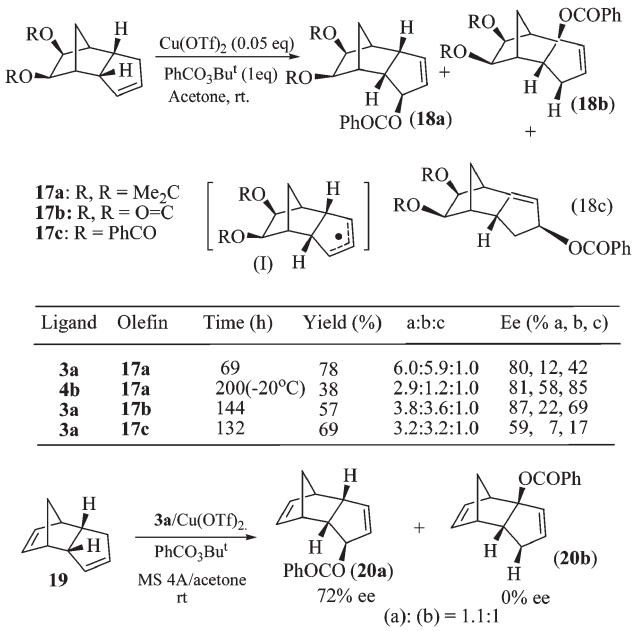
anticipated that the structure of the catalytic intermediate might be different in the case of trisoxazoline **4**.[14] Thus, trisoxazoline **4** was synthesized by Katsuki *et al.* and applied to the same reaction. It should be noted that the sense of enantiofacial selection in the oxidation of cyclopentene by ligand **4a** (65% ee, (*R*)) was opposite to that by using **3a** (76% ee, (*S*)) under the same reaction conditions, although the structures (stereochemistries) of the oxazoline units in ligand **3a** and **4a** were the same. This fact suggested that the geometry of copper ion ligated by **4a** was different from that by **3a**. Generally, under optimized reaction conditions, trisoxazoline **4b** had broader substrate scope, and could achieve higher enantiomeric excesses and yields in the oxidation of cycloalkene **16b–d** (Scheme 12).

Trisoxazolines **5** derived from Kemp's acid were also used in the allylic oxidation of the cyclopentene **16a**,[15] and the phenyl-substituted ligand **5a** proved to be better than its analogues **5b–c**, but only moderate ee was obtained [94% yield and 45% ee (*S*)].

Based on the mechanistic insight of the Kharash–Sosnovsky reaction, it was anticipated that the oxidation of racemic dioxygenated dicyclopentadiene or dicyclopentadiene would afford the optically active allyl benzoate bearing multiple stereogenic centres.[14,23] Accordingly, Katsuki *et al.* tried ligands **3a** and **4a** in the copper(II)-catalyzed oxidative desymmetrization of racemic dicyclopentadiene derivatives, which might proceed *via* the desymmetrization of a *meso*-allyl radical intermediate ((I), Scheme 13). For the reaction of racemic dioxygenated dicyclopentadienes **17** (Scheme 13) with various diol protecting groups, the allylic oxidation product **18** was obtained in moderate to high enantioselectivity (59–87% ee) using chiral catalyst trisoxazoline **3a**/$Cu(OTf)_2$, however, the regioselectivity of this reaction was not satisfactory. Ligand **4a** also afforded similar results in this reaction (Scheme 13). ^{t}Bu-BOX was also tested but afforded poorer yield and selectivity in this reaction.

Oxidative desymmetrization of dicyclopentadiene **19** mediated by ligand **3a** provided at best a 1.1:1.0 mixture of the product **20a** and **20b** with 72% ee for **20a** at room temperature (Scheme 13). ^{t}Bu-BOX achieved similar results in this reaction.

Allylic amination. Based on the mechanism of allylic oxidation, it was expected that allylic amination might proceed



Ligand	Olefin	Time (h)	Yield (%)	a:b:c	Ee (% a, b, c)
3a	**17a**	69	78	6.0:5.9:1.0	80, 12, 42
4b	**17a**	200(-20°C)	38	2.9:1.2:1.0	81, 58, 85
3a	**17b**	144	57	3.8:3.6:1.0	87, 22, 69
3a	**17c**	132	69	3.2:3.2:1.0	59, 7, 17

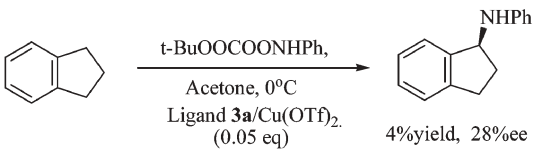
Scheme 13

in the same way. After successfully establishing methods for achiral amination, Katuski *et al.* also tried ligand **3a** in the corresponding asymmetric reaction (Scheme 14).[24] Initial studies showed that using **3a**/$Cu(OTf)_2$ as the chiral catalyst, low enantioselectivity (28%) and a poor yield (4%) was observed in this amination of an alkene using *N*-phenylperoxy-carbamate as oxidant at 0 °C in acetone. ^{t}Bu-BOX was also tested in this reaction, but only 7% ee obtained with 3% yield.

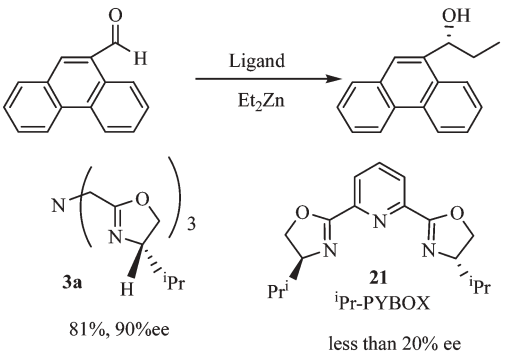
The addition of Et_2Zn to aldehyde. Chang *et al.* not only developed a new route to prepare trisoxazoline **3b**, but applied it to the addition of Et_2Zn to aldehyde.[13] It was found that up to 90% ee was obtained in the case of anthryl substituted aldehyde (Scheme 15). Noticeably, tridentate (*N*,*N*,*N*) ^{i}Pr-PYBOX afforded only 20% ee in this case under the same reaction condition, suggesting that chiral space created by trisoxazoline **3a** was more effective in this reaction than the relative bisoxazoline.

Kemp's acid derived trisoxazolines **5** had also been tried in this addition, but the optimum isopropyl-substituted ligand **5c** could only afford moderate ee (43% ee (*R*) in 46% yield).[15]

Friedel–Crafts reaction. Considering the structure difference between bisoxazoline and pseudo-C_3-symmetric trisoxazoline **8**, TOX **8a** was first tried in the Friedel–Crafts reaction of indole with alkylidene malonates. This asymmetric reaction was pioneered by Jørgensen *et al.* and they found that



Scheme 14

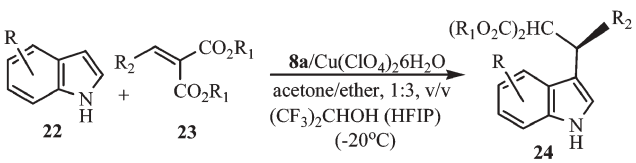


Scheme 15

tert-butyl-BOX/$Cu(OTf)_2$ afforded up to only 69% ee.[25] Initial study revealed that water- and air-stable chiral catalyst **8a**/$Cu(ClO_4)_2{\cdot}6H_2O$ could promote this reaction in up to 93% ee and 99% yield in a mixed solvent of acetone and ether (1/3, v/v), with the aid of two equivalents of HFIP relative to malonates **23** to accelerate the reaction (Scheme 16).[18]

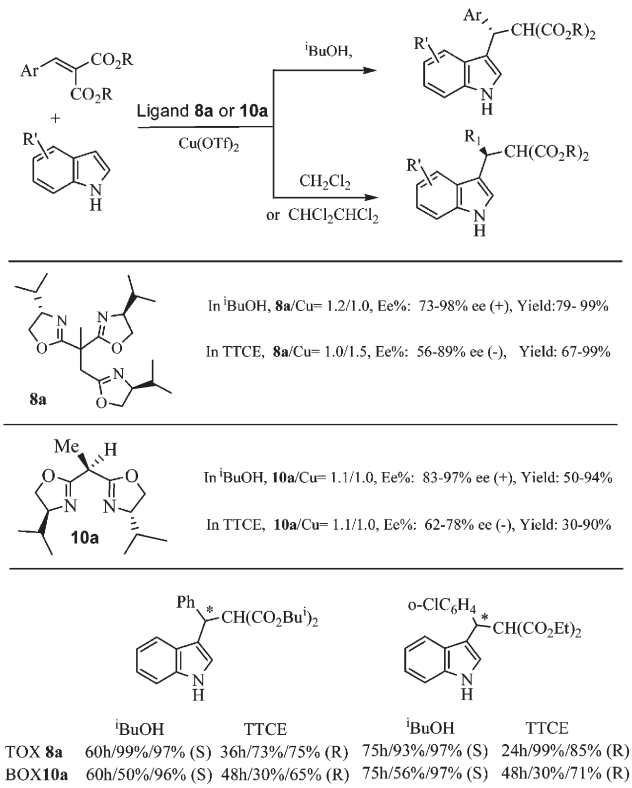
In the exploration of the role of HFIP, it was found that use of alcohols as the solvent could greatly accelerate this reaction and allow for the reaction to be carried out whilst exposed to air. Furthermore, the enantioselectivity for *S*-enantiomer was found to be dependent on the size of alcohol solvent, the bulkier the alcohol the better the enantioselectivity (see control experiment B in Scheme 18). The best improvement, up to 98% ee for *S*-enantiomer, was achieved when using isobutyl alcohol as the solvent at −25 °C.[26]

Very interestingly, a reversal of enantioselectivity was observed just by changing reaction solvent from coordinating solvents to weakly coordinating solvents such as halogenated solvents, using the same ligand **8a** and the same Lewis acid $Cu(OTf)_2$.[26,27] After careful screening of the solvents, ligands, copper salts, temperature and the ratio of ligand and $Cu(OTf)_2$, it was found that when 1,1,2,2-tetrachloroethane (TTCE) as the solvent at 0 °C, with the ratio of ligand **8a** to $Cu(OTf)_2$ being 1.0:1.5 (NOT 1.2:1.0!), up to 89% ee for the *R*-enantiomer was obtained (Scheme 17).



22	23	Yield (%)	Ee(%)
22a: R = H,	**23a**: R_1 = Me, R_2 = Ph	98	88
22a: R = H,	**23b**: R_1 = Et, R_2 = Ph	84	89 (S)
22b: R = 4-methoxy,	**23b**: R_1 = Et, R_2 = Ph	97	91
22c: R = 5-methoxy,	**23b**: R_1 = Et, R_2 = Ph	73	91
22d: R = 5-methyl,	**23b**: R_1 = Et, R_2 = Ph	92	93
22a: R = H, R_1 = Et,	**23c**: R = 2-ClPh	99	92
22a: R = H, R_1 = Et,	**23d**: R = 4-ClPh	84	90
22a: R = H, R_1 = Et,	**23e**: R = 3-NO_2Ph	99	91
22a: R = H, R_1 = Et,	**23f**: R = 4-NO_2Ph	99	91
22a: R = H, R_1 = Me,	**23g**: R = 4-NO_2Ph	99	91
22a: R = H, R_1 = Et,	**23h**: R_2 = Me (-78°C)	84	85

Scheme 16



	iBuOH	TTCE	iBuOH	TTCE
TOX **8a**	60h/99%/97% (S)	36h/73%/75% (R)	75h/93%/97% (S)	24h/99%/85% (R)
BOX**10a**	60h/50%/96% (S)	48h/30%/65% (R)	75h/56%/97% (S)	48h/30%/71% (R)

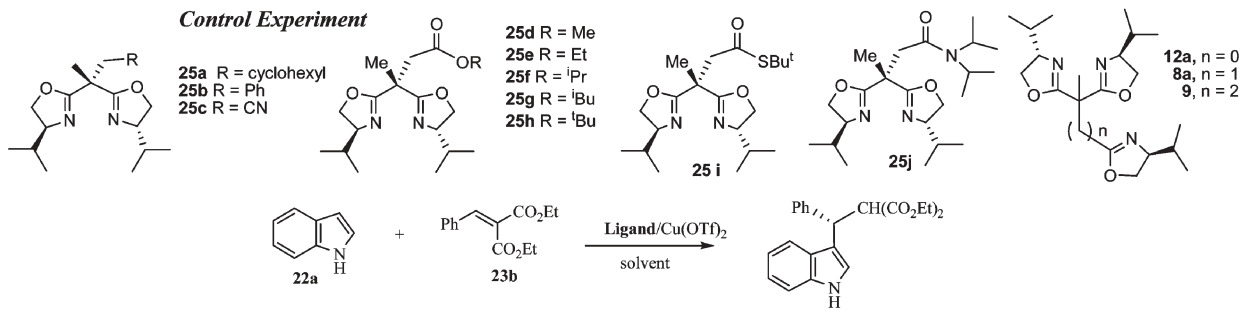
Scheme 17

During studying the reaction mechanism, we also developed a highly tunable and enantioselective indole alkylation with alkylidene malonates using cheap and simple bisoxazoline **10a** (Scheme 17). This made a detailed comparison possible between trisoxazoline **8a** and bisoxazoline **10a**.[28]

Generally, trisoxazoline **8a**/Cu(II) complexes had higher catalytic activity compared to bisoxazoline **10a**, better enantiofacial control and broader substrate scope could be achieved, as well as better enantioselectivity in milder reaction conditions. We list two examples in Scheme 17 for a brief comparison: Under the same reaction conditions, although the ee for the *S*-enantiomer is similar in iBuOH, BOX **10a** afforded obviously poorer yield; in TTCE, BOX **10a** was significantly inferior to TOX **8a** with respect to both reactivity and enantioselectivity. Furthermore, BOX **10a** could only achieve above 90% ee (for the *S*-enantiomer) at low temperature (−25 °C) using iBuOH, whereas TOX **8a** could achieve the same levels of enantioselectivity even at 15 °C.

Unexpectedly, (*N*,*N*,*N*) tridentate ligand iPr-PYBOX **21** failed to catalyze this reaction either in iBuOH or in TTCE.

It was believed that the coordination of the side-arm oxazoline to the copper centre significantly improved the catalytic properties (both electronic and steric), compared to its bisoxazoline congener. To testify this hypothesis, we synthesized a variety of bisoxazoline **25**,[19] substituting the third oxazoline ring by a range of functional group side-arms. Evaluation of side-arm effects was judged for the model reaction of indole **22a** with benzylidene malonate **23b**.[19] Results shown in Scheme 18 strongly supported the coordination of the side-arm oxazoline of TOX **8a** to the copper centre. In THF, when a non-coordinating bulky group such as Ph and cyclohexyl were employed as a side-arm, only moderate ee (37 and 48%) was obtained; in sharp contrast, even the relatively small coordinating side-arm a cyano group improved the ee to 61%. Furthermore, the bulkier the coordinating side-arm, the better the ee. The length of the side-arm oxazoline also significantly influenced both the reactivity and enantioselectivity (A, Scheme 18), These results supported the idea that



A: Evaluation of the side-arm effects in THF

Ligand	**25a,**	**25b,**	**25c,**	**25d,**	**25e,**	**25f,**	**25g,**	**25h,**	**25i,**	**25j,**	**12a,**	**8a,**	**9**
Ee% (+)	48	37	61	73	72	73	74	79	80	72	67	82	60

B: Solvent effect for S-enantiomer

Solvent	THF,	MeOH	EtOH	*i*-PrOH	*i*-BuOH
TOX **8a** (ee%):	82,	48	63	88	90
BOX **10a** (ee%):	53,	60	76	79	82

All reactions were carried out at 15°C using 10 mol% of catalyst

C: Counterion Effect in TTCE

8a/Cu(ClO$_4$)$_2$6H$_2$O = 1.0/1.5	KOTf/Cu = 0, 35%ee KOTf /Cu = 5, 74%ee
8a/Cu(OTf)$_2$ = 1.0/1.5	KOTf /Cu = 0, 80%ee (R)
10a/Cu(ClO$_4$)$_2$6H$_2$O = 1.2/1.0	KOTf/Cu = 0, 35%ee KOTf/Cu = 1, 74%ee
10a/Cu(OTf)$_2$ = 1.2/1.0	KOTf /Cu = 0, 74%ee (R)

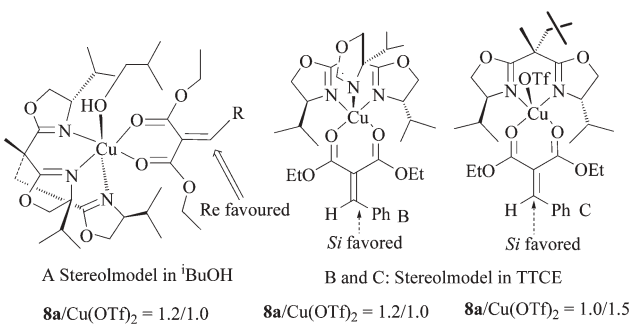
All reactions were carried out at 0°C using 10 mol% of catalyst

Scheme 18

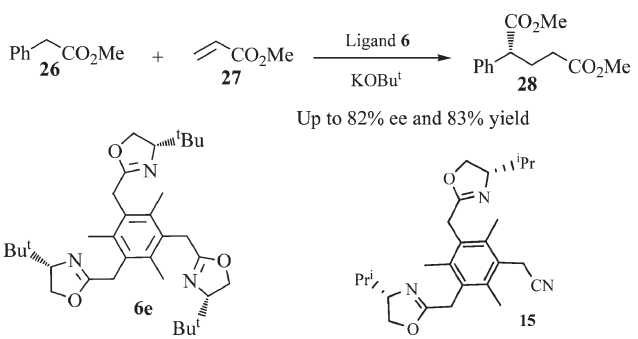
coordination of the side-armed oxazoline in TOX **8a**, tuned the electronic and steric properties of the catalyst to influence the enantioselectivity and reactivity.

The reversal of enantioselectivity from changing solvents might originate from the change of the coordination geometry of the copper centre. In isobutyl alcohol, considering the size of the alcohol significantly influenced the ee for the *S*-enantiomer (B, Scheme 18), the copper centre might form an octahedron (A, Scheme 19), due to the coordination of tridentate ligand, bidentate substrate and one equivalent of ^{i}BuOH. In TTCE, the copper centre is proposed to be a distorted square-pyramid (B and C, Scheme 19) in a bidentate fashion (taking into account the ratio of ligand and $Cu(OTf)_2$ is 1.0:1.5!), with one triflate counter-ion coordinated to copper centre (C, Scheme 18).[26]

Michael addition. Ahn *et al.* tried trisoxazoline (BTO) **6** in the Michael addition of methyl phenylacetate to methyl acrylate (Scheme 20). This work was based on their finding for molecular recognition that BTO had a significant affinity towards K^+ ion, which led them to evaluate these compounds as chiral ligands in the catalytic asymmetric reactions involving K^+ complexes such as potassium enolates. They found that *tert*-butyl-substituted BTO **6e** in combination with KOBu^t could promote the reaction of phenylacetate with methyl acrylate in up to 82% ee, using toluene as solvent at −78 °C.[29] The author proposed that ligand **6e** coordinated to the potassium enolate in a tripodal fashion *via* the oxazoline nitrogen atoms by two control experiments: first, bisoxazoline **15** failed to promote this reaction; second, BTO **6e** in combination with NaOBu^t proved to be unsuccessful in this reaction.



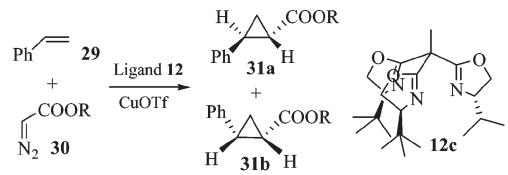
Scheme 19



Scheme 20

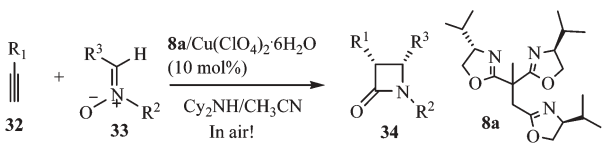
Cyclopropanation. Gade *et al.* examined the C_3-symmetric trisoxazolines **12** in copper catalyzed asymmetric cyclopropanation. Noticeably, hetero substituted trisoxazoline **12c** achieved better enantioselectivity than the other three ligands used for the cyclopropanation of styrene with ethyl diazoacetate. Up to 69/31 *trans*/*cis* selectivity and 86% ee for *trans* product was achieved (Scheme 21).[20] Although this result did not surpass that which was obtained by bisoxazolines,[1] it revealed an important fact that heterochiral trisoxazolines might be more versatile than homochiral trsioxazolines giving better compatibility with catalytic intermediates thus achieving higher enantiofacial control. To this end, the introduction or combination of different substituents at the oxazoline rings, chiral or achiral units or oxazolines with opposite absolute configuration within the same tripodal ligand system might be effective in creating a good chiral cleft for those reactions where it has been difficult to obtain satisfactory selectivities.

Kinugasa reaction. This reaction was developed in 1972, and is regarded as a promising protocol for the preparation of β-lactams. However, the previously reports were all focused on the use of Cu(I) salts as the catalyst, which required this reaction to be performed strictly under an inert atmosphere to mitigate the Glaser oxidative coupling. Fortunatly, we found for the first time that Cu(II) salts worked well in this reaction (Scheme 22). Trisoxazoline **8a**/$Cu(ClO_4)_2{\cdot}6H_2O$ could promote



	R = ^{t}Bu			R = Et		
L*	*cis*:*trans*	ee (*cis*, %)	ee (*trans*, %)	*cis*:*trans*	ee (*cis*, %)	ee (*trans*, %)
12a	22:78	70	65	29:71	64	67
12b	19:81	73	70	31:69	68	70
12c	23:77	85	80	31:69	81	86
12d	22:78	72	66	29:71	72	78

Scheme 21



Entry	R^1	R^2/R^3	*cis*/*trans*	Ee (*cis*, %)	Yield(%)
1	Ph	Ph/Ph	94/6	82	56
2	Ph	o-MeC_6H_4/Ph	95/5	82	36
3	Ph	o-$MeOC_6H_4$/Ph	97/3	84	36
4	Ph	o-BrC_6H_4/Ph	93/7	74	70
5	Ph	o-$EtO_2CC_6H_4$/Ph	91/9	70	98
6	Ph	Ph/o-MeC_6H_4	95/5	82	50
7	Ph	Ph/o-$MeOC_6H_4$	95/5	83	58
8	Ph	Ph/o-$CF_3C_6H_4$	93/7	82	75
9	Ph	Ph/2-Furanyl	67/33	85	56
10	Ph	Ph/Ph	96/4	84	35
11	p-CF_3Ph	Ph/Ph	75/25	73	65
12	cyclohexyl	Ph/Ph	93/7	72	35

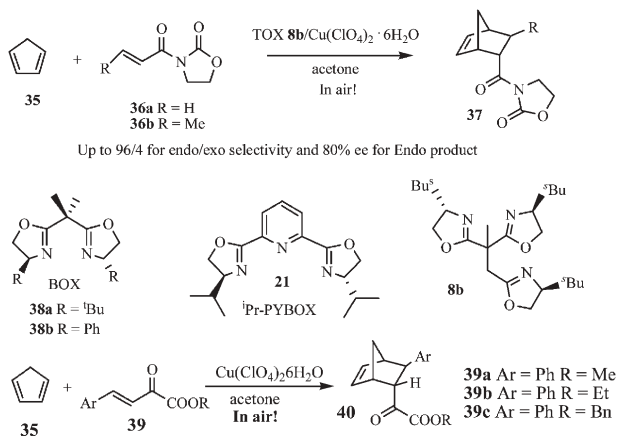
Scheme 22

this reaction well under an aerobic atmosphere.[30,31] Bases were found to strongly influence the course of the reaction. Up to 97/3 *cis*/*trans* selectivity and 85% enantioselectivity for *cis* isomer was achieved when the secondary amine dicyclohexylamine was used as a base.

Diels–Alder reaction. Pseudo-C_3-symmetric trisoxazoline **8** also proved useful in the copper catalyzed Diels–Alder reaction of cyclopentadiene **35** with 2-oxazolidinone **36** or ketoesters **39**. After careful screening of Lewis acids, solvents, anions, temperature and ligands, ^{s}Bu-substituted trisoxazoline **8b**/$Cu(ClO_4)_2{\cdot}6H_2O$ complex in acetone was found to afford up to 80% ee for the *endo* product (96/4 *endo*/*exo*) in the case of oxazolidinone **36**, and 71% ee for *endo* product (97/3 *endo*/*exo*) in the case of ketoester **39**. This reaction could also be carried out exposed to air![32] Several frequently used bisoxazolines were also examined in the cycloaddition of cyclopentadiene with ketoesters. However, *tert*-butyl and phenyl substituted BOX **38a** and **38b** failed to achieve better results than trisoxazoline **8b**. (Scheme 23). Noticeably, ^{i}Pr-substituted PYBOX **21** showed much lower catalytic activity than other ligands, higher temperatures (0 °C) were required to complete the reaction, whilst −35 °C was sufficient for others.

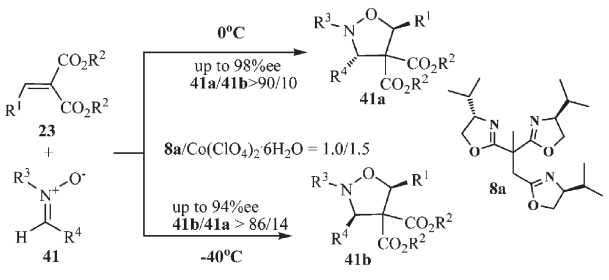
1,3-Dipolar cycloaddition. Pseudo-C_3-symmetric TOX **8a** in combination with $Co(ClO_4)_2{\cdot}6H_2O$ also proved to be an excellent chiral catalyst for 1,3-dipolar cycloaddition of nitrones **41** with alkylidene malonates **23** (Scheme 24).[33] In this case, much better enantioselectivity was obtained when the ratio of trisoxazoline **8a** and $Co(ClO_4)_2{\cdot}6H_2O$ was 1.0/1.5 rather than 1.2/1.0, the same feature was also observed in the synthesis of the *R*-enantiomer in the indole alkylation shown in Scheme 16.[26]

The outstanding characteristic of this reaction was that the *endo*/*exo* selectivity could be controlled effectively by changing reaction temperature so that both *cis*-and *trans*- isoxazolidines



Entry	Ligand	39	Temp(°C)	Time (h)	Yield (%)	Endo/exo	Ee% (endol)
1	**38a**	**39a**	-35	48	52	8/92	53
2	**38b**	**39a**	-35	48	58	8/92	0
3	**21**	**39a**	0	48	63	12/88	4
4	**8b**	**39a**	-35	48	64	3/97	71
5	**8b**	**39b**	-35	48	82	3/97	64
6	**8b**	**39c**	-35	48	47	3/97	62

Scheme 23



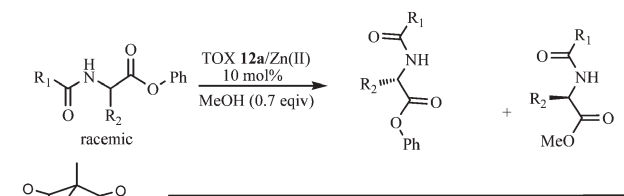
Entry	R_1/R_2	R_3/R_4	0°C Yield(%)	41b/41a	Ee(%)	-40°C Yield(%)	41b/41a	Ee(%)
1	*p*-BrC_6H_4/Et	Ph/Ph	99	95/5	95	88	5/95	80
2	*p*-$NO_2C_6H_4$/Et	Ph/Ph	93	97/3	94	99	10/90	83
3	*p*-MeC_6H_4/Et	Ph/Ph	95	95/5	92	99	14/86	88
4	Ph/Et	Ph/Ph	94	97/3	95	81	11/89	93
5	Ph/Et	*p*-MeC_6H_4/Ph	94	99/1	91	77	14/86	87
6	Ph/Et	*p*-BrC_6H_4/Ph	76	99/1	95	90	10/90	80
7	Ph/Bu^{i}	*p*-BrC_6H_4/Ph	95	99/1	96	38	12/88	94
8	c-Hex/Et	*p*-BrC_6H_4/Ph	91	90/10	89	99	14/86	71

Scheme 24

could be prepared enantioselectively.[33] At 0 °C, the *exo* isomers of isoxazolidines were obtained with both high enantioselectivity and *exo*/*endo* selectivity. Interestingly, when the temperature was lowered from 0 to −40 °C, the same cycloaddition afforded *endo* isomers as the major products with good to high enantioselectivity. A possible mechanism for this reversal of diastereoselectivity by temperature was also proposed on the basis of control experiments. It was concluded that reaction to form *cis*-isoxazolidine was reversible and subject to kinetic control at −40 °C, while at 0 °C, the cycloaddition was subject to thermodynamic control, favouring the *trans* isomer.

Kinetic resolution by transesterification. Most recently, Gade *et al.*[34] applied their C_3-symmetric trisoxazoline **12a** derived zinc complex as a functional model for kinetic resolution of racemic chiral esters by transesterification (Scheme 25).

This was the first example of a non-enzymatic catalyst for asymmetric transesterification of activated esters. Anions of the zinc cation obviously influenced the selectivity factors [S = (rate of the fast-reacting enantiomer)/(rate of the slow-reacting enantiomer)]. Upon changing from the zinc triflate to the acetate complex and further to the trifluoroacetate



Entry	Substrate	Selecting factors (*S*) $Zn(OTf)_2$	$Zn(OAc)_2$	$(CF_3CO_2)_2Zn$
1	R_1 = Ph, R_2 = Ph	1.8	3.5	3.8
2	R_1 = Ph, R_2 = Me	1.3	2.7	3.0
3	R_1 = Me, R_2 = Me	2.0	4.5	5.1
4	R_1 = Me, R_2 = Bn	1.8	2.6	4.3

Scheme 25

complex, there was an increase of the selectivity factor for all the substrates, noticeably up to $S = 5.1$ for entry 3.

The importance of the tripodal-zinc chiral environment for the accomplished enantioselectivity was inferred from the fact that the use of classical bidentate BOX **38c**/Zn(II) does not induce kinetic resolution.

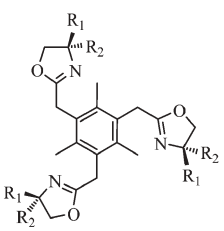
Trisoxazolines in molecular recognition

Molecular recognition has been the focus of intense research interest, partly for elucidating a better understanding of recognition phenomena in nature, and also for potential applications in separation processes, catalysis, sensing and biochemical studies. Recently, the application of benzene-based trisoxazolines in molecular recognition, mainly contributed by the Ahn group, turned out to be especially promising for the selective recognition of NH_4^+, alkylammonium ions, and the enantiomeric recognition of α-chiral primary ammonium ions and β-chiral primary ammonium ions.

Selective recognition of K^+ over NH_4^+. The selective recognition of NH_4^+ from monovalent metal cations, especially K^+, is an important issue in clinical chemistry and has attracted much interest. The commercially used recognition component, Nonactin, only provides a slight preference for NH_4^+ over K^+ (selectivity <10). Ahn *et al.* first applied their benzene-based TOX **6** in this area,[35] and found that the association constants and their relative magnitude between NH_4^+ and K^+ were dependent on the oxazoline structure (Scheme 26). Methyl-substituted TOX **6b** exhibited the largest association constant toward NH_4^+. X-Ray diffraction analysis of a single crystal of the host–guest complex revealed that the oxazoline nitrogens were providing directional hydrogen bonds toward three ammonium NH bonds. The three directional hydrogen bonds by the oxazoline ligands and the presumed cation–π interactions by the benzene ring were believed to be the reasons that produced the high selectivity for the recognition of NH_4^+ over K^+.

Recognition of alkylammonium ions. The recognition system for alkylammonium ions such as n-butylammonium and *β*-phenethylammonium ions is very important in clinical application because they are the structural motifs in biologically important amines such as GABA and dopamine. Based on their previous finding that the NH_4^+-binding affinity was dependent on the oxazoline substituents, Ahn *et al.* tried the selective recognition of alkylammonium ions by optimizing the steric and electronic properties of the oxazoline substituents (Scheme 27).[16]

They found that, compared with isopropyl, benzyl substituted TOX **6a** and **6d**, phenyl-substituted receptor **6c** achieved high association constants for alkylammonium ions (Scheme 28), and the $^nBuNH_3^+/^tBuNH_3^+$ selectivity was as high as *circa.* 710. Considering that receptors capable of favourable preorganization are expected to enhance the binding affinity, TOX **6g–h** were also developed. For TOX **6h**, the selectivity was further enhanced to 4000. By X-ray crystallographic and ^1H NMR studies of the host–guest complex, the significant binding affinity and high selectivity observed with TOX **6c** and the related derivatives **6g–h** was attributed to the optimized steric and electronic environment provided by these ligands: 1) In addition to the hydrogen bonds, there existed cation–π interactions between the ammonium ion and the benzene framework which might stabilize the complex; 2) Hydrophobic interactions provided

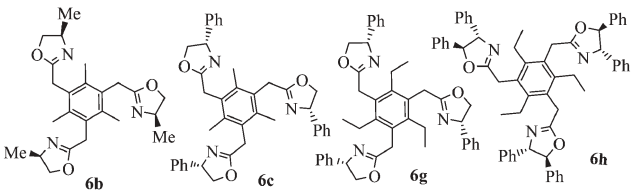


Association Constants (Ka x 10^{-3} M^{-1}) of NH_4^+ and K^+ (picrate salts) with receptor 6

	NH_4^+	K^+	NH_4^+/K^+
6a	9400	23.9	393
6b	25000	57.2	437
6h	3900	57	68
6n	5100	29.5	73
Nonactin	198000	7100	3

6a R_1 = *i*Pr, R_2 = H; **6b** R_1 = Me, R_2 = H
6h $R_1 = R_2$ = Me : **6n** $R_1 = R_2$ = H

Scheme 26

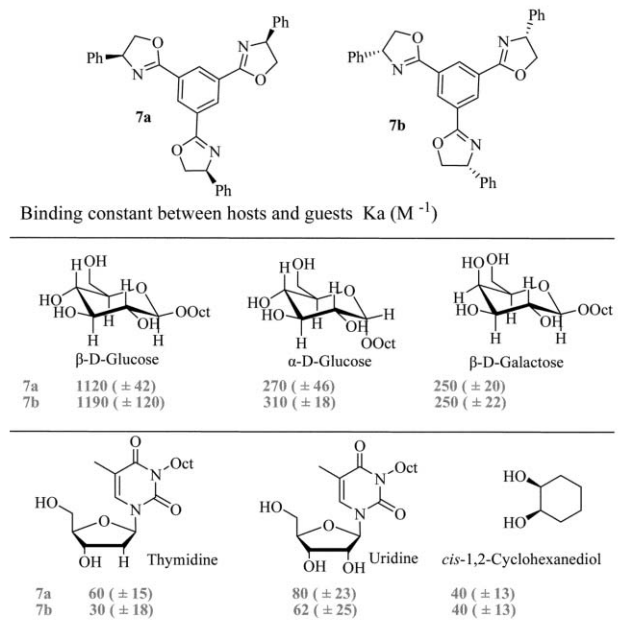


Association constant ($logK_{ass}$) of alkylammonium ions with TOX **6**

Receptor	$nBuNH_3^+$	$sBuNH_3^+$	$tBuNH_3^+$	$Ph(CH_2)_2NH_3^+$	$nBuNH_3^+/tBuNH_3^+$
6b	5.28	4.20	3.70	6.61	38
6c	6.65	6.65	3.80	#	710
6g	7.96	5.94	3.67	#	2700
6h	7.77	5.92	4.53	#	4000

Could not be determined due to very large deviations

Scheme 27



Binding constant between hosts and guests Ka (M^{-1})

	β-D-Glucose	α-D-Glucose	β-D-Galactose
7a	1120 (± 42)	270 (± 46)	250 (± 20)
7b	1190 (± 120)	310 (± 18)	250 (± 22)

	Thymidine	Uridine	*cis*-1,2-Cyclohexanediol
7a	60 (± 15)	80 (± 23)	40 (± 13)
7b	30 (± 18)	62 (± 25)	40 (± 13)

Scheme 28

by receptors **6c, g–h**, in which phenyl substituents of oxazoline rings encompass the guest, form a ''hydrophobic wall''.

Sugar recognition. With the knowledge that the three oxazoline nitrogens can act as H-bonding acceptors and a central aromatic group as a π-donor for CH–π interactions, Hong *et al.* focused on the application of their benzene-based TOX **7** to anomer-selective recogition for n-octyl-D-glucopyranoside.[17] As shown in Scheme 28, C_3-symmetric oxazolines **7** could serve as artificial receptors for sugar and alcohols. ^{1}H NMR titration in $CDCl_3$ showed a dramatic downfield shift of aromatic protons at the centre of ligand **7a**, which resulted from intermolecular hydrogen-bonding interactions between H-bond acceptor N of the host and H-bond donor OH of the guest. The selectivity between α- and β- anomers was up to 4.1 (β/α). The anomeric selectivity and diastereoselectivity for sugars might result from the slight energetic difference in the intermolecular H-bonding patterns between sugars and **7a**. Diols, *N*-octylthymidine and *N*-octyluridine exhibited weaker binding affinities to **7a**, probably due to fewer hydroxyl groups and therefore a lessened ability to form H-bonds.

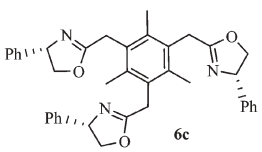
Recognition of α-chiral primary ammonium ions. The chiral recognition of α-chiral primary ammonium ions was mostly achieved in a C_1 or C_2-symmetric environment. Ahn *et al.* accomplished for the first time the enantiomeric recognition of α-chiral primary ammonium ions using C_3-symmetric benzene-based trisoxazoline **6** as the acceptor (Scheme 29).[36]

The chiral discrimination has been found to be general in the case of α-aryl substituted guests. Binding studies by NMR titration and isothermal titration calorimetry show that the chiral discrimination originated from the different thermodynamic stabilities between the diastereomeric complexes. Host–guest complex formation was driven by favourable enthalpy changes with a minor negative contribution by entropy changes. The authors successfully studied the single crystals of both of the diastereomeric inclusion complexes. XRD analysis revealed that the guest and oxazoline phenyl rings were well stacked, indicative of the interplay of π–π interactions. The role of π–π interactions was to restrict the conformational freedom of the guest and also increase the binding affinity, thereby endowing the receptors with good enantio-discriminating ability.

Recognition of β-chiral primary ammonium ions. There are few successful examples of enantio-discrimination of β-chiral primary amines *via* ammonium ions, partly due to the free rotation of β-chiral substituents away from the ammonium binding site. Based on work concerning recognition of α-chiral primary ammonium ions, Ahn *et al.* employed bifurcated H-bonding as an auxiliary interaction that could block the free rotation of β-substituents, and thus secured a chiral environment for the guest.[37]

As shown in Scheme 30, guests **1–3** with β-OH functionality acting as the H-bond acceptor exhibited chiral discrimination, while guest **4** without β-OH groups (methyl at the β-position for example) showed no selectivity, demonstrating the importance of the H-bond. When introducing carboxamide to the β-position as the H-bond acceptor such as in guests **7–9**, high levels of enantio-discrimination were also observed. X-ray diffraction data also substantiated the bifurcated H-bonding. Chiral molecular recognition with C_3-symmetric TOX **6c** was generally extended toward α-,β-, and α,β-chiral amines.[37]

Fluorescence sensing. In the course of applying the benzene-based TOX **6** to the molecular recognition of biologically active amines through the corresponding ammonium salts, Ahn *et al.* developed this system into a new class of

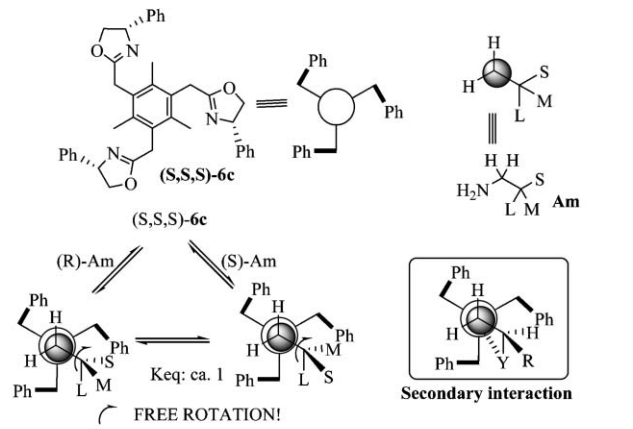


Enantioselective binding of TOX **6c** toward racemic ammonium salts

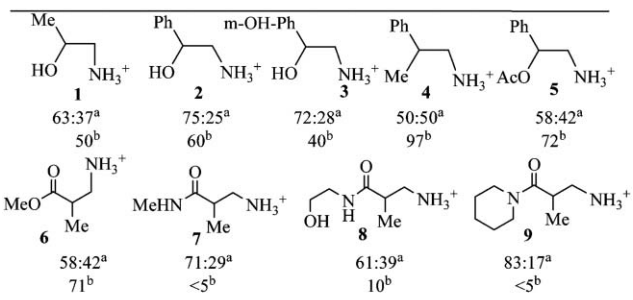
Racemic ammonium guest	Enantioselectivity[a]	Extraction
α-phenylethylamine	71 (R): 29 (S)	82
α-(1-naphthyl)ethylamine	70:30	99
phenylglycine methyl ester	78 (S) : 22 (R)	60
tryptophan methyl ester	67 (S) : 33 (R)	57
alanine methyl ester	53 (S) :47 (R)	41
phenylalanine methyl ester	55 (S) :45 (R)	36

[a]Ee of the ammonium ion extracted from excess racemic $RNH_3^+Cl^-$

Scheme 29



Selective binding of TOX **6c** toward racemic ammonium salts of ¦Âchiral amines



[a] Enantiomeric ratio of the extracted guest from excess racemic salts
[b] Percentage of the ammonium salt extracted into $CDCl_3$ with respect to TOX **6c**.

Scheme 30

fluorescence sensors for ammonium and organo-ammonium ions.[38] Methyl-substituted TOX **6b** showed a significant fluorescence enhancement upon binding NH_4^+. When titrating TOX **6b** with varying concentrations of NH_4^+ in acetonitrile at 295 K, the fluorescence intensity increased gradually and reached a plateau when an equimolar amount of NH_4^+ was added. Little change appeared with the addition of excess NH_4^+, suggesting the formation of a 1:1 host–guest complex. It should be noted that at the saturation point, the fluorescence intensity amounted to 2.75 times that of the receptor only. In contrast, little response toward K^+, Na^+ and Mg^{2+} cations was observed, which might be due to the lower binding affinity of TOX **6b** toward metal cations compared to NH_4^+.

Since phenyl-substituted TOX **6c** was able to selectively recognize organo-ammonium ions,[16,35–36] it was also subjected to fluorescence measurements upon binding $PhCH_2CH_2NH_3^+$ (as the perchlorate salt),[38] the maximum enhancement was 1.72 times larger. The TOX **6c** was also applied in the enantioselective fluorescence sensing of both enantiomers of the perchlorate salts of 1-phenylethylamine, the fluorescence enhancement was larger in the case of the *R*-salt.

Conclusion and outlook

With increased ligand diversity, a more tunable chiral space and electronic properties, trisoxazolines have attracted increasing interest as documented by the current research efforts. In asymmetric catalysis, trisoxazolines turned out to be excellent ligands for some reactions, not only in achieving high enantioselectivities, but also for the fact that trisoxazoline derived catalyst proved to be stable to water and air in some cases, which allowed some reactions to be performed in aerobic conditions. These promising properties are deemed to be due to the introduction of the pendant oxazoline. In addition, in some trisoxazoline–metal complex catalyzed reactions, reactivity and stereoselectivity could be tuned by using different reaction conditions and/or with the change of the ratio of the ligand and Lewis acid. This might be a unique characteristic of trisoxazoline at least in contrast to their bisoxazoline congeners, likely originating from the change in both the aggregation state of chiral catalyst and preorganization of chiral catalyst-substrate. Another merit of trisoxazolines was that they enabled cheap chiral sources with small steric extensions to achieve excellent enantioselectivities, for example, satisfactory selectivity was often achieved when L-valinol derived ligands were used, while in bisoxazoline systems, *tert*-butyl substituted ligands proved to be superior in most cases. In molecular recognition studies, some trisoxazolines were highly selective for recognition of NH_4^+, alkylammonium ions, α-chiral primary ammonium ions and β-chiral primary ammonium ions. The main drawback associated with trisoxazolines is that, to some extent, they can be more challenging to synthesize than their C_2-symmetric bisoxazoline analogues. With the introduction of modular syntheses and new synthetic methodogy, however, synthetic problems should no longer be an obstacle to the prosperity of trisoxazolines. Compared to bisoxazoline chemistry, reports detailing mechanistic studies associated with trisoxaozlines are relatively limited, an area which needs to be strengthened to provide more information for the development of trisoxazoline related chemistry. Nevertheless, it can be anticipated that studies concerning the development and application of trisoxazolines will keep providing new and exciting results in asymmetric catalysis, molecular recognition and other fields in the future.[39]

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