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Catalytic enantioselective 1,3-dipolar cycloaddition reactions of nitrones

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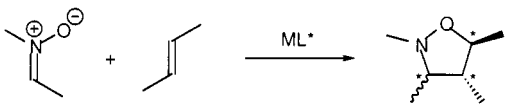
The rapid developments in the field of catalytic enantioselective 1,3-dipolar cycloaddition reactions of nitrones which have occurred during the last six years are reported. A series of catalysts has been applied for both the normal electron-demand and inverse electron-demand 1,3-dipolar cycloaddition reaction of nitrones with electron-deficient and electron-rich alkenes, respectively. In several cases a high degree of control of both the diastereo- and enantioselectivity has been achieved.

Introduction

After the Diels–Alder reactions, the second most important cycloaddition reaction is probably the 1,3-dipolar cycloaddition.[1] The 1,3-dipolar cycloaddition reaction of nitrones with alkenes in particular has received considerable attention in asymmetric synthesis over the past 15 years.[2,3] One of the reasons for the success of the synthetic application of nitrones is that, contrary to the majority of other 1,3-dipoles, most nitrones are stable compounds that do not require *in situ* formation. In the 1,3-dipolar cycloaddition reaction of nitrones with alkenes, up to three new contiguous chiral centers can be formed in the adduct (Scheme 1)[4,5] and the isoxazolidine formed can be



Scheme 1

transformed into numerous attractive building-block molecules for organic synthesis. The absolute majority of these 1,3-dipolar cycloaddition reactions are diastereoselective and involve chiral alkenes or nitrones.[2,3] It would, however, be highly desirable to develop a catalytic enantioselective version of this reaction. Compared to the successful development of the catalytic enantioselective Diels–Alder reaction in the late 1980s, the first examples of the catalytic enantioselective 1,3-dipolar cycloaddition reactions of nitrones did not appear until 1994.

In the early development of the catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones with alkenes the catalysts were 'borrowed' from Diels–Alder chemistry, but in the more recent developments a series of catalysts that are optimised for the 1,3-dipolar cycloaddition reaction have been developed. A few catalysts are highly selective for both types of reaction.

In this article we wish to present to the reader an overview of this field, which has gone through rapid developments during the last six years. Several research groups have been engaged in the area and it has been attempted to include all the major contributions in which catalytic enantioselective reactions have been described. The article is divided into two major parts: (*i*) the normal electron-demand reactions and (*ii*) the inverse electron-demand reactions, which are two fundamentally different approaches to the catalytic control of the reaction. A final short part (*iii*) describing alternative catalytic approaches to the reaction is also included.

Normal electron-demand reactions

The relative FMO energies of the substrates of the 1,3-dipolar cycloaddition reaction are important for catalytic control of the reaction.[2,6,7] In order to be able to control the stereochemistry of the reaction with a sub-stoichiometric amount of a ligand–metal catalyst it is desirable that large reaction rate accelerations are obtained to assure that the reaction only takes place in the sphere of the metal and the chiral ligand. The strategy that was applied for the catalytic enhancement of the reaction rate has therefore been to alter the relative energies of the FMOs of one of the substrates using chiral Lewis acids.[6] This principle of activation can be applied to the 1,3-dipolar cycloaddition of nitrones in two different ways. The normal electron-demand involves the reaction of a nitrone with an electron-deficient alkene such as an α,β-unsaturated carbonyl compound. This reaction is primarily controlled by the interaction between $HOMO_{nitrone}$–$LUMO_{alkene}$ (Fig. 1). By the application of a Lewis acid (LA) catalyst which acts as an electron acceptor, the LUMO energy of the alkene is lowered by coordination of the α,β-unsaturated carbonyl to the Lewis acid. As a result of the decreased energy gap between the interacting FMO's a rate acceleration of the reaction is achieved.[6]

One of the problems related to the Lewis-acid activation of α,β-unsaturated carbonyl compounds for reaction with a nitrone is the competitive coordination of the nitrone and the α,β-unsaturated carbonyl compound to the Lewis acid (Scheme 2).[6] Calculations have shown that coordination of the nitrone to the Lewis acid is more feasible than a monodentate coordination of a carbonyl compound. However, this problem could be

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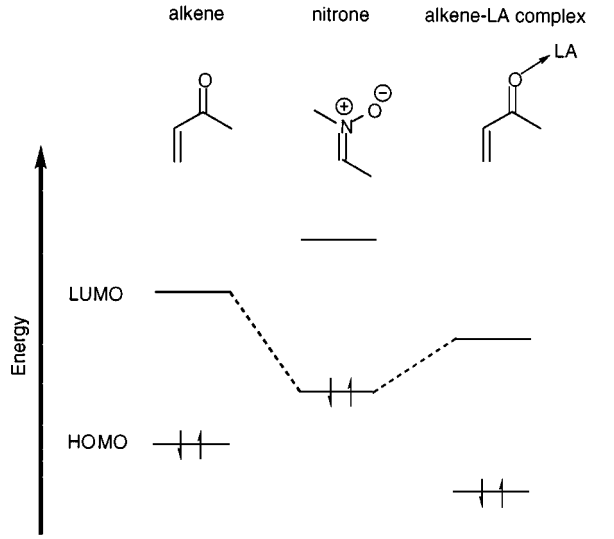
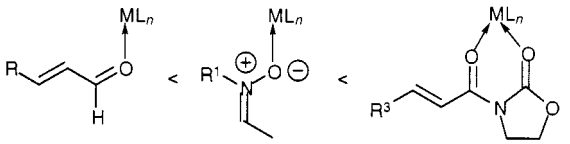


Fig. 1 The catalytic alteration of the alkene FMO's in the normal electron-demand 1,3-dipolar cycloaddition reaction.



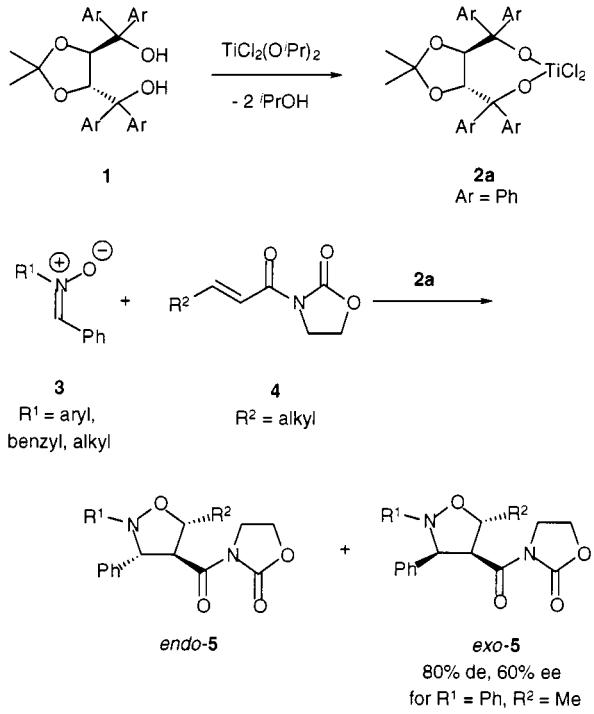
Scheme 2

circumvented by the application of alkenes such as 3-alkenoyl-oxazolidinones enabling a bidentate coordination to the Lewis acid which is favoured over the monodentate coordination.

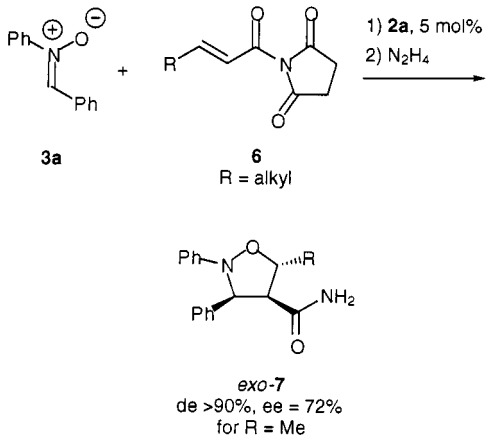
Titanium catalysts

Several titanium(IV) complexes are efficient and reliable Lewis acid catalysts and they have been applied to numerous reactions, especially in combination with the TADDOL (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) (**1**) ligands.[7–10] In the first study on normal electron-demand 1,3-dipolar cycloaddition reactions between nitrones and alkenes, which appeared in 1994, the catalytic effect of a series of chiral $TiCl_2$–TADDOLates on the reaction of nitrones **3** with alkenoyl-oxazolidinones **4** was studied (Scheme 3).[11] These substrates have turned out to be the model system of choice for most studies on Lewis-acid catalysed normal electron-demand 1,3-dipolar cycloaddition reactions of nitrones. When 10 mol% of the catalyst **2a** was applied in the reaction depicted in Scheme 3 the reaction proceeded to give a yield of up to 94%. The reaction led primarily to *exo*-**5** and in the best case an *endo*:*exo* ratio of 10:90 was obtained. The chiral information of the catalyst was transferred with a fair efficiency to the substrates as up to 60% ee of one of the isomers of *exo*-**5** was obtained.[11]

In the majority of $TiCl_2$–TADDOLate catalysed Diels–Alder and 1,3-dipolar cycloaddition reactions oxazolidinone derivatives are applied as auxiliaries for the alkenoyl moiety in order to obtain the favourable bidentate coordination of the substrate to the catalyst.[12] In a more recent study on 1,3-dipolar cycloaddition reactions the use of succinimide instead of the oxazolidinone auxiliary was introduced (Scheme 4).[13] The succinimide derivatives **6** are more reactive than **4** in the 1,3-dipolar cycloaddition reaction with nitrone **3a**. In the presence of the $TiCl_2$–TADDOLate catalyst **2a** (5 mol%), the reaction of **3a** with **6** (R = Me) gives *exo*-**7** as the only diastereomer. Additionally, the enantioselectivity of the reaction of 72% ee is also an improvement compared to the analogous reaction of the oxazolidinone derivative **4**. Similar improvements were obtained in reactions of other related nitrones.



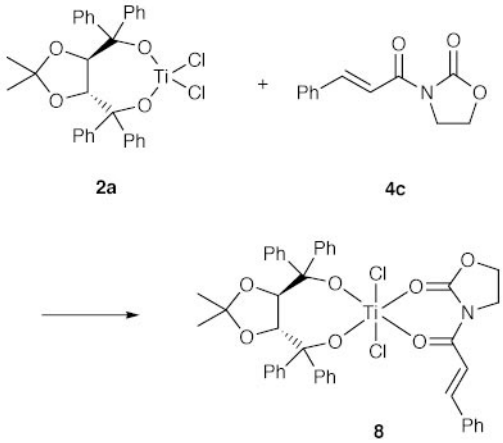
Scheme 3

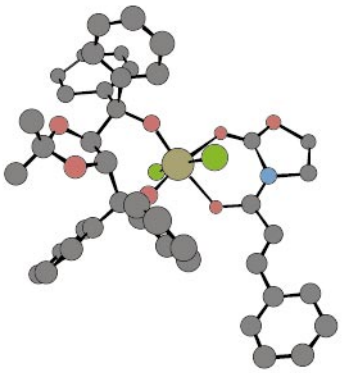


Scheme 4

In connection with the investigations of the $TiCl_2$–TADDOLate-catalysed 1,3-dipolar cycloaddition reactions between nitrones and alkenoyloxazolidinones, a complex between the chiral titanium catalyst and the alkene substrate **4c** was isolated (Scheme 5).[14] This crystalline compound **8** was characterised by X-ray crystallography and the X-ray structure showed that the oxazolidinone is coordinated to the titanium center in a bidentate fashion. The four oxygen atoms, two from the chiral ligand and two from **4c**, are located in a plane around the titanium center, while the two chloride ligands are located in the apical positions. This crystal structure is a highly valuable verification of how the mechanism of the catalytic activation is operating. To some extent, information can also be derived about how one of the faces of the alkene is shielded by the ligand leading to the enantioselective addition of the nitrone to the opposite face of the alkene. However, there are several other possible arrangements of the ligands around the titanium center and whether **8** actually represents the reactive intermediate has been the subject of some dispute.[15–18]

Based on the structure of intermediate **8**, investigations of the impact on the *endo/exo*-selectivity in the 1,3-dipolar cycloaddition reaction of changing the chloride ligands in the $TiCl_2$–TADDOLate catalyst **2a** to bulkier groups were performed.[19] In Table 1 some results of reactions between **3a** (R^1 = Ph) and **4a**





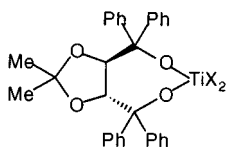
3D structure of **8**
(hydrogens are omitted for clariety)

Scheme 5

Table 1 Application of TiX_2–TADDOLate **2a–d** as catalyst for the 1,3-dipolar cycloaddition reaction between **3a** (R^1 = Ph) and **4a** (R^2 = Me) (Scheme 3)

Entry	Catalyst	Catalyst amount	Conversion (time)	*endo*:*exo*	Ee *endo* (*exo*) (%)
1	**2a**	10	98% (48)	10:90	62 (60)
2	**2b**	10	98% (20)	64:36	76 (64)
3	**2c**	10	73% (20)	79:21	0
4	**2d**	50	99% (48)	>95:<5	93

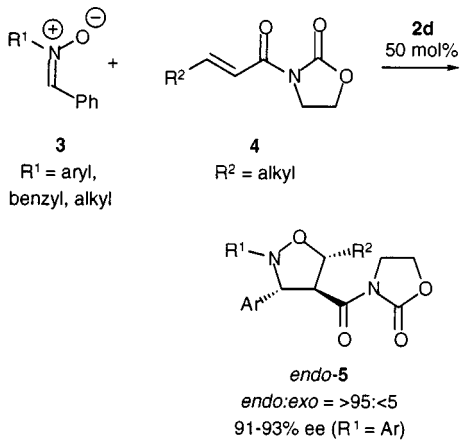
(R^2 = Me) in the presence of various TiX_2–TADDOLate catalysts are listed (see reaction in Scheme 3). By the application of **2b**, the bromide analogue to **2a**, the diastereoselectivity changes (entry 2). This reaction proceeds with a low *endo*-selectivity. Using the triflate analogue **2c**, leads to an *endo*-selective reaction (entry 3). Unfortunately, this reaction was racemic. For the reaction of **3a** and **4a** in the presence of tosylate catalyst **2d**, a high conversion is obtained (entry 4). The



2a: X = Cl
2b: X = Br
2c: X = OTf
2d: X = OTs

endo-selectivity of this reaction is excellent, and this was the first example of a metal-catalysed 1,3-dipolar cycloaddition reaction between nitrones and alkenes proceeding with more than 90% ee.

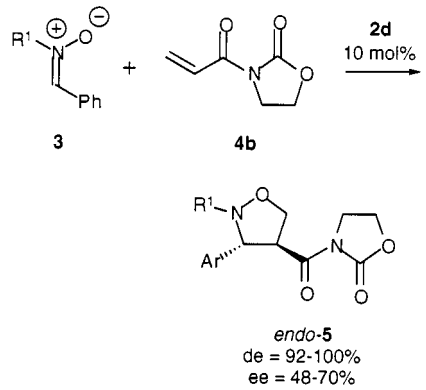
As an extension of the successful application of **2d**, this catalyst was applied in a series of reactions (Scheme 6). For all eight reactions of nitrones **3** and alkenes **4** in which **2d** was applied as the catalyst, diastereoselectivities >90% de were



Scheme 6

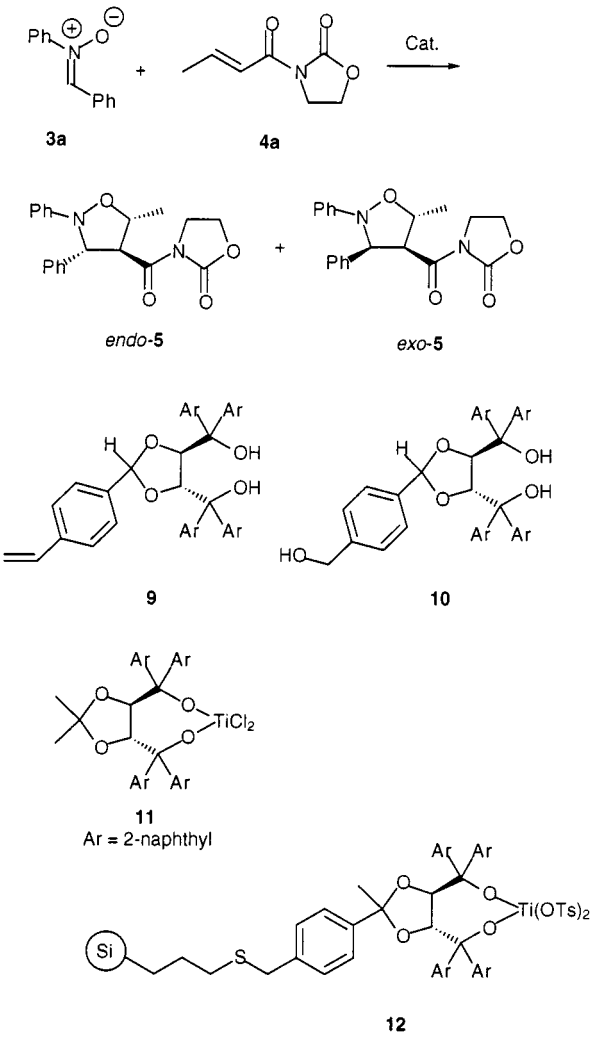
observed, and most remarkably >90% ee is obtained for all reactions involving a nitrone with an aromatic R^1 substituent, whereas reactions with *N*-benzyl and *N*-alkyl nitrones led to lower enantioselectivities.[19]

The TiX_2–TADDOLate catalysed 1,3-dipolar cycloaddition reactions were extended to include an acrylate derivative.[20] In the absence of a catalyst, the reaction between nitrone **3** and acryloyloxazolidinone **4b** proceeded to give a mixture of all eight regio-, diastereo- and enantiomers (Scheme 7). However, application of $Ti(OTs)_2$-TADDOLate **2d** (10 mol%) as catalyst for the reaction of various nitrones such as **3** with alkene **4b**, led to complete regioselectivity, high *endo*-selectivity, and the *endo*-products **5** were obtained with 48–70% ee (Scheme 7).[20]



Scheme 7

Seebach *et al.*, who first developed the TADDOL ligands,[7] have also developed a number of polymer- and dendrimer-bound $TiCl_2$–TADDOLate catalysts derived from the monomeric TADDOLs.[21] Application of 10 mol% of this type of catalyst, derived from polymers and dendrimers of **9** and **10**, respectively, in the reaction between nitrone **3a** and alkene **4a** led to *endo*:*exo* ratios between 18:82 and 8:92 and up to 56% ee (Scheme 8). The selectivities are thus slightly decreased compared to similar reactions of the homogeneous catalysts. They also made a study of the relationship between the enantiomeric purity of the ligand of the homogeneous catalyst **11**, and the products obtained in both the 1,3-dipolar cycloaddition reaction between **3a** and **4a** and in the Diels–Alder reaction of **4a** with cyclopentadiene. Surprisingly, the 1,3-dipolar cycloaddition shows a linear relationship, whereas the Diels–Alder reaction shows a positive non-linear relationship. In recent work Heckel and Seebach have studied the use and reuse of $Ti(OTs)_2$–TADDOLate catalysts immobilized on porous silica gel.[22] The selectivity obtained in the 1,3-dipolar cycloaddition reaction between nitrone **3a** and **4a** catalysed by **12**, was only slightly lower compared to the corresponding homogeneous reaction.[19] The same batch of the ligand in **12** could be



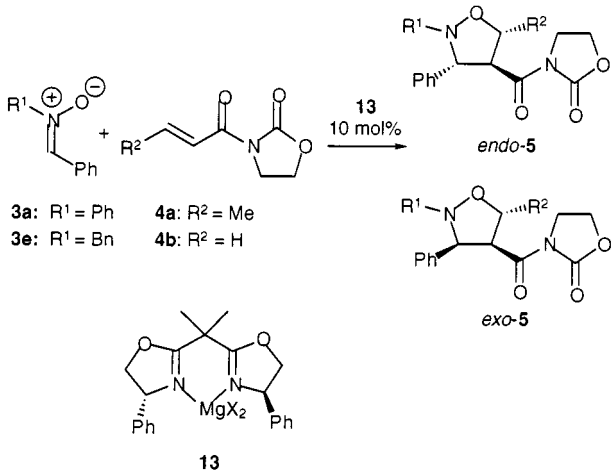
Scheme 8

used in four consecutive reactions with no significant loss of activity, when the ligand was carefully washed between the reactions.[22]

Magnesium catalysts

Prior to the first publication on chiral magnesium catalysts for 1,3-dipolar cycloaddition reactions in 1995, there had been several studies on the impact of non-chiral magnesium salts on the diastereoselectivities in cycloaddition reactions of both nitrones,[23–25] and nitrile oxides[26] with allylic alcohols.

In the first[27] and also the following[28–30] publications applying chiral magnesium catalysts, chiral bisoxazolines (BOX) were applied as the ligand for magnesium. The MgX_2–Ph-BOX catalyst **13** (X = I), proved to be a useful catalyst for the 1,3-dipolar cycloaddition between **3** and **4a**,**b** when it was activated by the addition of I_2 (Scheme 9).[27] Furthermore, the



Scheme 9

reaction had to be performed in the presence of molecular sieves (MS) 4 Å. In the presence of 10 mol% of **13** (X = I) the reaction proceeded with good to high *endo*-selectivity and the *endo*-isomer was obtained in an ee of up to 82% (Scheme 9, Table 2, entry 1).

A rather unexpected discovery was made during these investigations.[28] When the 1,3-dipolar cycloaddition reaction of **3a** with **4b** catalysed by **13** (X = I) was performed in the absence of MS 4 Å a remarkable reversal of enantioselectivity was observed, as the opposite enantiomer of *endo*-**5** was obtained in up to 73% ee (Table 2, entries 1, 2). This had not been observed for enantioselective catalytic reactions before and the role of MS cannot simply be ascribed to the removal of water by the MS, since the application of MS 4 Å that were presaturated with water, also induced the reversal of enantioselectivity (Table 2, entries 3, 4). Recently, Desimoni *et al*. found that in addition to the presence of MS in the MgX_2–Ph-BOX catalysed 1,3-dipolar cycloaddition reaction shown in Scheme 9, the counter ion for the magnesium catalyst also strongly affects the absolute stereoselectivity of the reaction.[29,30] They applied MgX_2–Ph-BOX **13** (X = ClO_4, OTf) complexes and compared the results with the MgX_2–Ph-BOX **13** (X = I) catalyst. It was observed that both in the presence and absence of MS, the catalyst **13** (X = ClO_4) gave the opposite absolute configuration of the product compared to the reaction of catalyst **13** (X = I) (Table 2, entries 5, 6). For catalyst **13** (X = OTf), the reaction was racemic in the presence of MS, whereas a high enantioselectivity of 86% ee was obtained in the absence of additives. The absolute configuration of the product of the reaction catalysed by **13** (X = OTf) in the absence of MS was similar to that obtained with **13** (X = ClO_4) catalyst and opposite to that obtained with **13** (X = I) (entries 2, 6 and 8).[29]

It should also be mentioned that in relation to the investigations on MgX_2–BOX catalysts, Desimoni *et al*. also tested a $Zn(ClO_4)_2$–BOX catalyst for the 1,3-dipolar cycloaddition of a nitrone and acryloyloxazolidinone **4b** (see Scheme 9). Contrary

Table 2 Dependence of the absolute stereoselectivity on molecular sieves (MS) and counter ion in the reaction of **3a** with **4b** catalysed by 10 mol% of MgX_2–Ph-BOX catalysts **13**

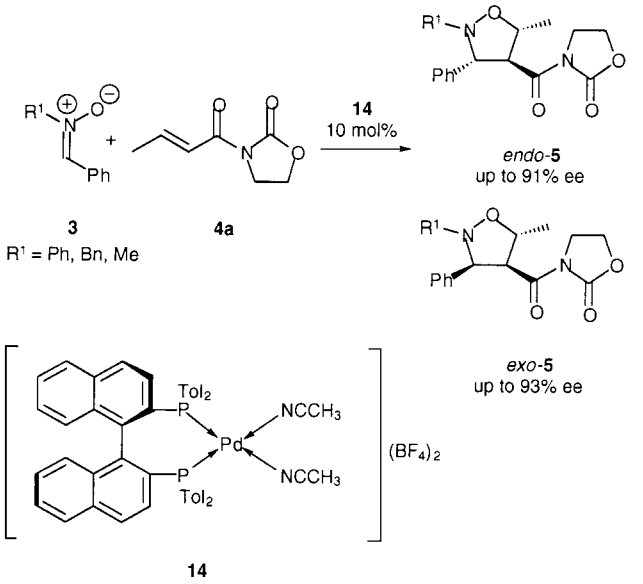
Entry	MgX_2-counter ion	Additive	*endo*:*exo* (%)	Ee *endo* (%)	Absolute induction	Ref.
1	I	MS 4 Å	73:27	82	3*S*,4*R*	28
2	I	—	100:0	48	3*R*,4*S*	28
3	I	H_2O	90:10	36	3*R*,4*S*	28
4	I	MS 4 Å, H_2O	95:5	36	3*S*,4*R*	28
5	ClO_4	MS 4 Å	70:30	70	3*R*,4*S*	29,30
6	ClO_4	—	95:5	48	3*S*,4*R*	29,30
7	OTf	MS 4 Å	56:44[a]	2	—	29,30
8	OTf	—	97:3	86	3*S*,4*R*	29,30

[a] Mixture of regiomers obtained.

to the magnesium catalysts, this zinc catalyst was *exo*-selective as a 27 : 73 *endo* : *exo* ratio was obtained, with 84% ee of the *exo*-isomer.[30]

Palladium catalysts

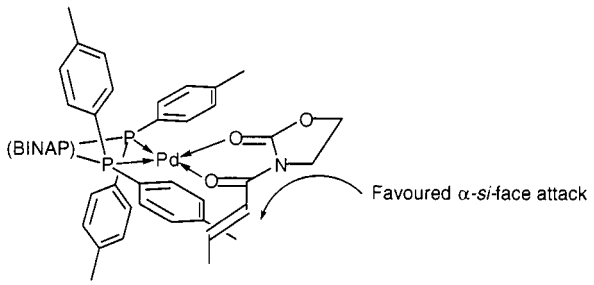
For the activation of a substrate such as **4a** *via* coordination of the two carbonyl oxygen atoms to the metal, one should expect that a hard Lewis acid would be most suitable, since the carbonyl oxygens are hard Lewis bases. Nevertheless, Furukawa *et al*. succeeded in applying the relatively soft d^{10} palladium as the catalyst for the 1,3-dipolar cycloaddition reaction between **3** and **4a** (Scheme 10).[32,33] They applied the



Scheme 10

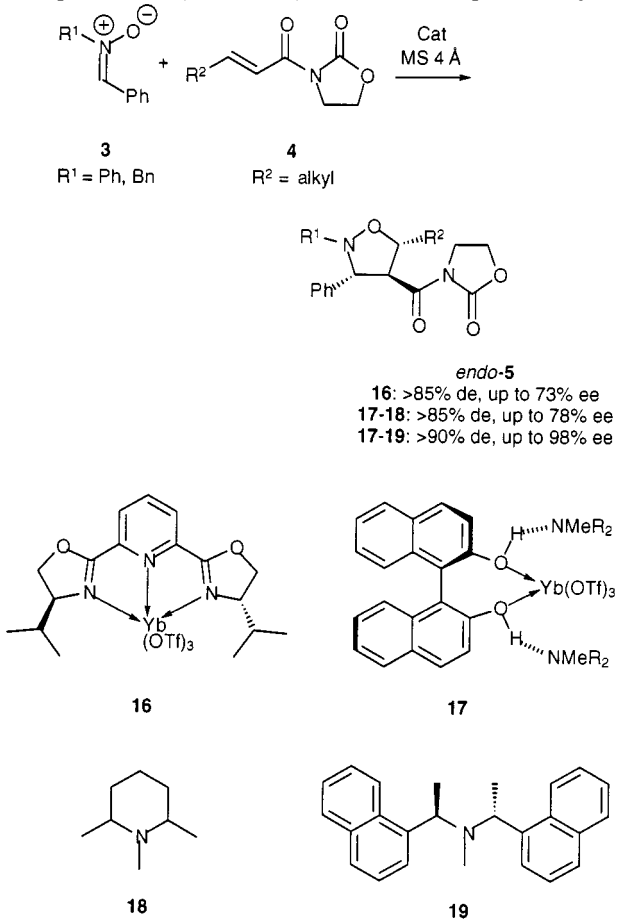
dicationic Pd–BINAP **14** as the catalyst, and whereas this type of catalytic reaction is often carried out at room temperature, the reactions catalysed by **14** required heating at 40 °C in order to proceed. In most cases mixtures of *endo*-**5** and *exo*-**5** were obtained, however, high enantioselectives of up to 93% ee were obtained for reactions of some derivatives of **3**.

A model **15** for the intermediate of the reaction was proposed to account for the high selectivities obtained for some of the substrates.[33] In **15**, the two phosphorous atoms of the Tol-BINAP ligand and the two carbonyl oxygens of the crotonoyloxazolidinone are arranged in a square planar fashion around the palladium center (note that the counter ions are omitted from this model). From the model it appears that the upper *si*-face of the alkene is sterically available for the cycloaddition reaction, while the *re*-face is shielded by one of the Tol-BINAP *p*-tolyl groups.



Lanthanide catalysts

In 1997 the application of two different chiral ytterbium catalysts, **16** and **17**, to the 1,3-dipolar cycloaddition reaction was reported almost simultaneously by two independent research groups.[34,35] In both reports, it was observed that the achiral $Yb(OTf)_3$ and $Sc(OTf)_3$ salts catalyse the 1,3-dipolar cycloaddition between nitrones **3** and alkenoyloxazolidinones **4** with *endo*-selectivity. In the first study 20 mol% of the $Yb(OTf)_3$–PyBOX complex **16** was applied as the catalyst for reactions of a number of derivatives of **3** and **4**. The reactions led to *endo*-selective 1,3-dipolar cycloadditions giving products with up to 73% ee (Scheme 11).[34] In the other report, Kobayashi

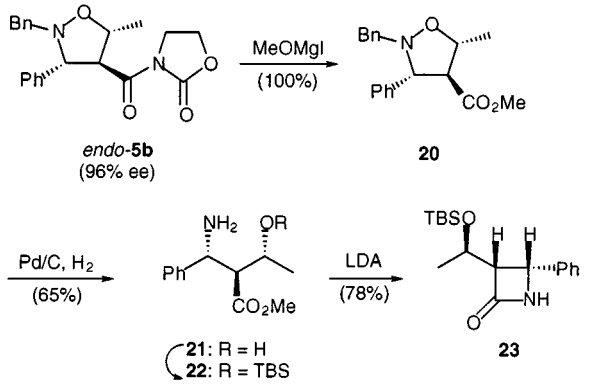


Scheme 11

et al. described a 1,3-dipolar cycloaddition catalysed by 20 mol% of the $Yb(OTf)_3$–BINOL complex **17** in the presence of the achiral tertiary amine **18**.[35] In this approach the nitrone **3** (R^1 = Bn) was formed *in situ* from the respective aldehyde and hydroxylamine. High *endo*-selectivities were observed, and for one derivative the product *endo*-**5** was obtained with 78% ee.[35] In an extension of these investigations the 1,3-dipolar cycloaddition reaction was performed in the presence of 20 mol% of the catalyst **17** and 40 mol% of the chiral amine **19**.[36] By substituting the achiral amine **18** with the chiral amine **19**, the selectivity of the reaction was improved significantly. For the reactions of some derivatives of **3** and **4**, *endo*-**5** was obtained as a single diastereomer and with up to 96% ee. Further investigation in this field by Kobayashi *et al*. led to the finding that the absolute stereoselectivity of the reaction was reversed when the reaction was performed in the absence of MS 4 Å.[37] This observation is analogous to the MgX_2–BOX catalysed reactions, where a similar incidence was observed.[28] In the reaction catalysed by **17** using **19** as the additive, *endo*-**5** (R^1 = Bn, R^2 = Me) was obtained in 96% ee in the presence of MS 4 Å. In the absence of MS 4 Å the opposite enantiomer was obtained in 50% ee. This inverse selectivity could be improved by using various *N*-oxides as a third additive.[37]

Whereas there are numerous examples of the application of the products from the diastereoselective 1,3-dipolar cycloaddition reactions in synthesis,[2,3] there are only very few examples

of the application of the products from catalytic enantioselective 1,3-dipolar cycloaddition reactions in the synthesis of potential target molecules. The reason for this may be due to the fact that most asymmetric metal-catalysed 1,3-dipolar cycloaddition reactions have been carried out on model systems that have not been optimised for further derivatisation. One exception of this is the elegant and short synthesis of a β-lactam by Kobayashi and Kawamura.[36] The isoxazolidine *endo*-**5b**, which was obtained in 96% ee from the $Yb(OTf)_3$–BINOL catalysed 1,3-dipolar cycloaddition reaction, was converted into the ester derivative **20**, quantitatively (Scheme 12). Hydrogenation over

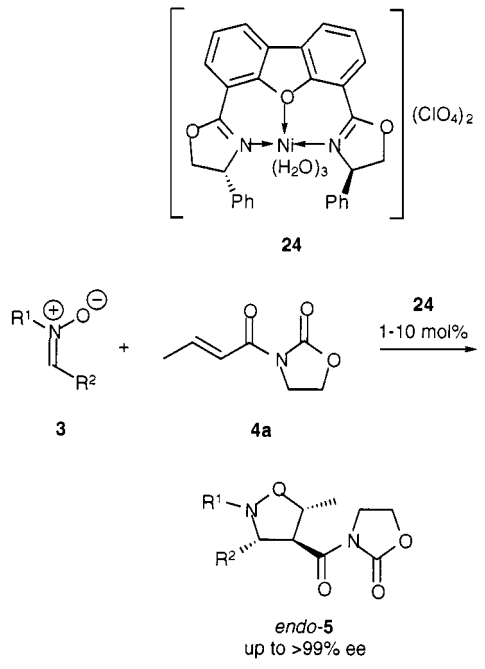


Scheme 12

palladium on carbon opens the isoxazolidine ring and cleaves the *N*-benzyl moiety to give **21**. Following a silyl protection of the hydroxy group to obtain **22**, the final ring-closure is mediated by LDA to give the β-lactam **23** in a high yield with a conserved optical purity of 96% ee.

Nickel catalysts

In 1998 Kanemasa *et al.* published the structure of dibenzofuranyl-2,2′-bisoxazoline (DBFOX) which has proved to be an excellent new ligand for a variety of Lewis acids.[38] The catalytic reactions that have been developed using this type of Lewis acid–DBFOX complex include catalytic 1,3-dipolar cycloaddition reactions of nitrones.[39] The $Ni(ClO_4)_2$–DBFOX/Ph complex **24** (Scheme 13) is a quite remarkable Lewis acid



Scheme 13

catalyst as it can be formed from the aqueous $Ni(ClO_4)_2 \cdot 6H_2O$ salt and the ligand. The water can be removed by the addition of MS 4 Å. The reaction between different nitrones **3** and crotonoyloxazolidinone **4a** proceeded in the presence of 1–10 mol% of the dicationic nickel complex **24** as the catalyst. Although long reaction times were required to obtain good yields, the reactions proceeded, in most cases, with very high *endo*-selectivities, and in several cases > 99% ee of the *endo*-products **5** was obtained. So far this catalyst is undoubtedly the most selective catalyst for the normal electron-demand 1,3-dipolar cycloaddition reaction between nitrones and alkenes, especially with respect to the enantioselectivity of the reaction.[39]

The inverse electron-demand reactions

The other catalytic approach to the 1,3-dipolar cycloaddition reaction is the 'inverse electron-demand', in which the nitrone is activated for addition to an electron-rich alkene such as, for example, a vinyl ether (Fig. 2). In this scenario the $FMO's_{alkene}$

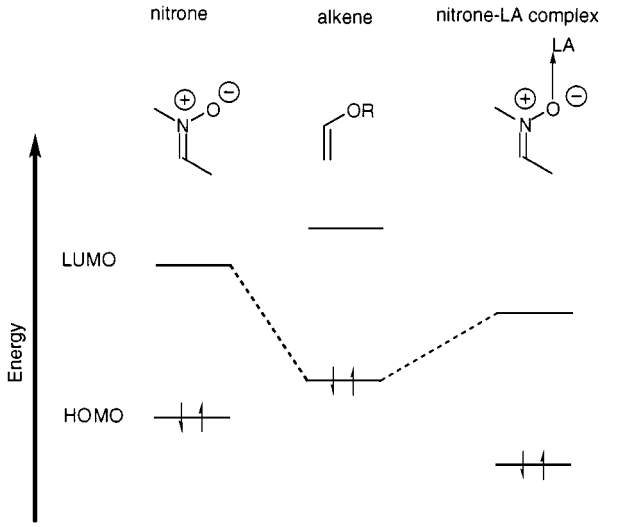


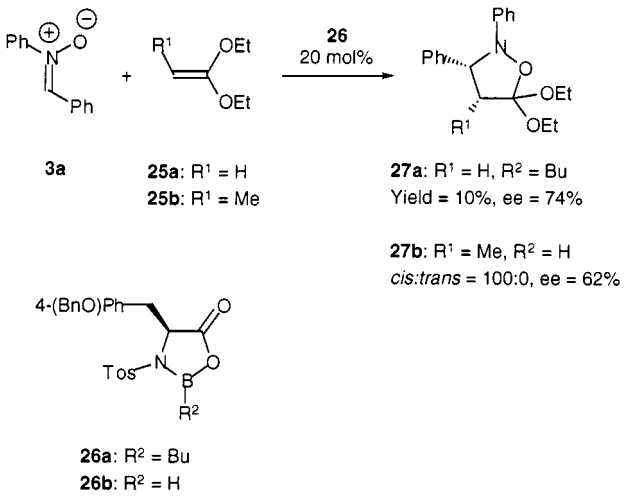
Fig. 2 The catalytic alteration of the nitrone FMO's in the inverse electron-demand 1,3-dipolar cycloaddition reaction.

have higher energies than the $FMO's_{nitrone}$ and the dominating interaction in the reaction will be $LUMO_{nitrone}$–$HOMO_{alkene}$. The nitrone can coordinate to the Lewis acid, leading to a decrease of the $LUMO_{nitrone}$ energy. The decreased energy gap between the two FMO's responsible for the dominating interaction leads to an enhanced rate of the 1,3-dipolar cycloaddition reaction of nitrones.

Boron catalysts

Scheeren *et al.* reported the first catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones with alkenes in 1994.[40] Their approach involved *C*,*N*-diphenylnitrone **3a** and ketene acetals **25**, and the amino acid derived oxazaborolidinones **26** were applied as the catalyst (Scheme 14). This type of boron catalyst has been used successfully for asymmetric Diels–Alder reactions.[41,42] In this reaction the nitrone is activated, according to the inverse electron-demand, for a 1,3-dipolar cycloaddition with the electron-rich alkene. They found that coordination of the nitrone to the boron Lewis acid strongly accelerated the 1,3-dipolar cycloaddition reaction with ketene acetals. The reactions of **3a** with **25a**,**b** were catalysed by 20 mol% of oxazaborolidinones such as **26a**,**b**. Fair enantioselectivities were induced and **27a** was obtained with an optical purity of 74% ee, however, in a low yield. The reaction involving **25b** gave the *C*-3,*C*-4-*cis*-isomer **27b** as the only diastereomer of the product with 62% ee.

In an extension of this work Scheeren *et al.* studied a series of derivatives of *N*-tosyl-oxazaborolidinones as catalysts for the 1,3-dipolar cycloaddition reaction of **3a** with **25b**.[43] The



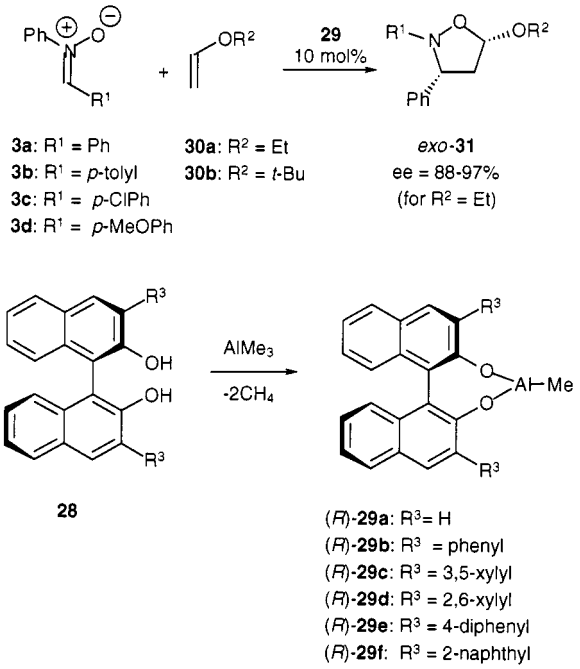
Scheme 14

addition of a co-solvent appeared to be of major importance. Catalyst **26b** was synthesized from the corresponding amino acid and BH_3·THF, hence, THF was present as a co-solvent. In this reaction (−)-**27b** was obtained with 62% ee. If the catalyst instead was synthesized from the amino acid and BH_3·SMe_2, and diphenyl ether was added, a remarkable reversal of the enantioselectivity of the reaction occurred, since (+)-**27b** was now obtained as the major isomer. Furthermore, the ee in this approach was improved to 79%. In more recent work the same research group has applied cyclic and acyclic vinyl ethers in the oxazaborolidinone catalysed 1,3-dipolar cycloaddition reaction with nitrones.[44] High diastereoselectivities were obtained, however, the highest enantioselectivity was 38% ee. In an analogous study by Meske, the impact of various oxazaborolidinone catalysts for the 1,3-dipolar cycloaddition reactions between acyclic nitrones and vinyl ethers was studied.[45] The highest enantioselectivity obtained in this work was 20% ee.

Aluminium catalysts

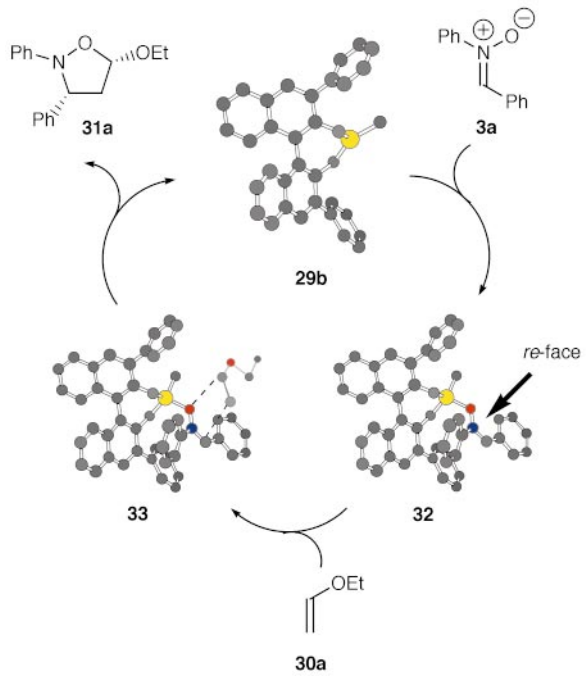
As for boron catalysts, the aluminium catalysts have exclusively been applied for the inverse electron-demand 1,3-dipolar cycloaddition between alkenes and nitrones. The first contribution to this field was published in 1999.[46] The initial catalytic experiments were performed using the AlMe–BINOL catalyst **29a**, that was simply synthesised by mixing the chiral BINOL ligand **28a** with $AlMe_3$ (Scheme 15). This catalyst was applied for the reaction between nitrone **3a** and vinyl ethers **30a**,**b**. A large rate enhancement was observed by using this catalyst, although, the selectivity of the reactions was rather disappointing. As part of these studies a new method for the synthesis of 3,3′-aryl substituted BINOL ligands **28b**–**f** was developed.[47] The introduction of substituents in the ligands 3,3′-position as in catalysts **29b-f** led to a remarkable improvement of the selectivities when these catalysts were applied in the reaction of **3a** with **30b** (Scheme 15). In particular, complex **29b** possessed the desired properties as the reaction performed in the presence of 20 mol% of this catalyst was completed within 45 min to give *exo*-**31b** (R^1 = Ph, R^2 = *t*-Bu) as the only observable diastereomer with 89% ee. The best results were achieved by applying the ethyl vinyl ether **30a** in the reaction instead of **30b**. The reactions between a series of nitrones **3a**–**d** with **30a** catalysed by 10 mol% of **29b** all proceeded to give the corresponding products **31** with excellent *exo*-selectivities and with enantioselectivities of 88–97% ee.[46]

A model for the mechanism of the highly enantioselective AlMe–BINOL-catalysed 1,3-dipolar cycloaddition reaction was proposed as illustrated in Scheme 16. In the first step nitrone **3a** coordinates to the catalyst **29b** to form intermediate **32**. In this intermediate, which is proposed to account for the absolute stereoselectivity of the reaction, it is apparent that one



Scheme 15

of the faces of the nitrone, the *si*-face, is shielded by the ligand, whereas the *re*-face remains available for reaction with ethyl vinyl ether **30a** as shown in **33**. The high *exo*-selectivity may also be explained by the model. As appears from the step in which **30a** approaches the nitrone–catalyst complex **33**, the ethoxy moiety of **30a** is pointing away from the nitrone *N*-phenyl group which leads to formation of the *exo*-isomer of the product **31a**. The assignment of the absolute configuration of the product was in full agreement with the *re*-face selectivity proposed in this model.[46]



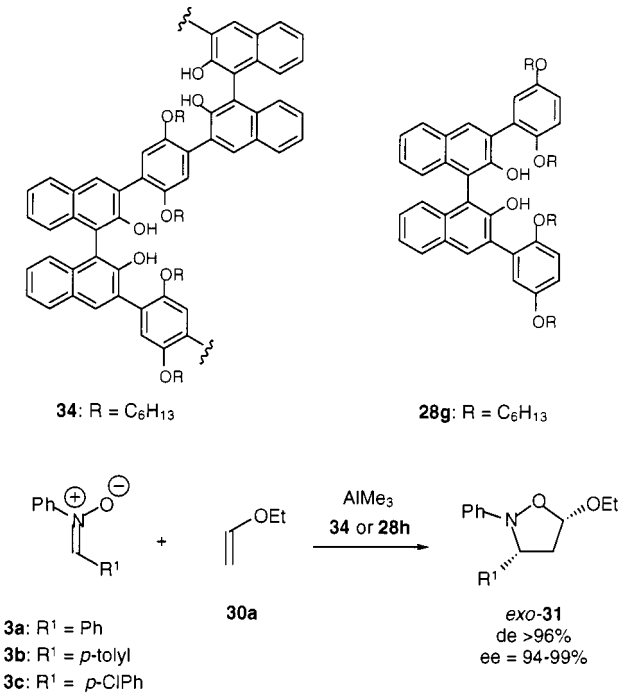
Scheme 16

Pu *et al.* have developed a new type of rigid polymer of 1,1-binaphthols.[48–50] The 3,3′-crosslinked polymeric binaphthol ligand **34** in combination with $AlMe_3$ was applied as the catalyst for the 1,3-dipolar cycloaddition (Scheme 17).[51] Very high selectivities were obtained when the aluminium catalyst of **34** (20 mol%) was applied to the 1,3-dipolar cycloaddition reaction of nitrone **3a** with alkene **30a**. The only observable

diastereomer resulting from the reactions was *exo*-**31a** (R^1 = Ph) and it was obtained with an enantioselectivity as high as 99% ee. One of the advantages of using a polymeric catalyst is the easy removal and recovery of the ligand from the reaction. Upon completion of the reaction, the catalyst was hydrolysed and the ligand precipitated by addition of methanol. After evaporation of the solvent and the excess of **30a**, the pure product *exo*-**31a** was isolated in 97% yield. Similar excellent selectivities were obtained for reactions of other nitrones.

Another important advantage of using the polymeric ligand **34** is, in addition to the easy purification of the product, that the ligand can be isolated and reused after the simple precipitation procedure. In this manner a sample of the polymeric ligand was isolated and reused in four consecutive reactions of nitrone **3a** and ethyl vinyl ether **30a**. Both yield and enantioselectivity of *exo*-**31a** showed only slight decreases after the ligand had been reused. The slight decrease was ascribed to the loss of small amounts of the ligand during the recycling procedure.[51]

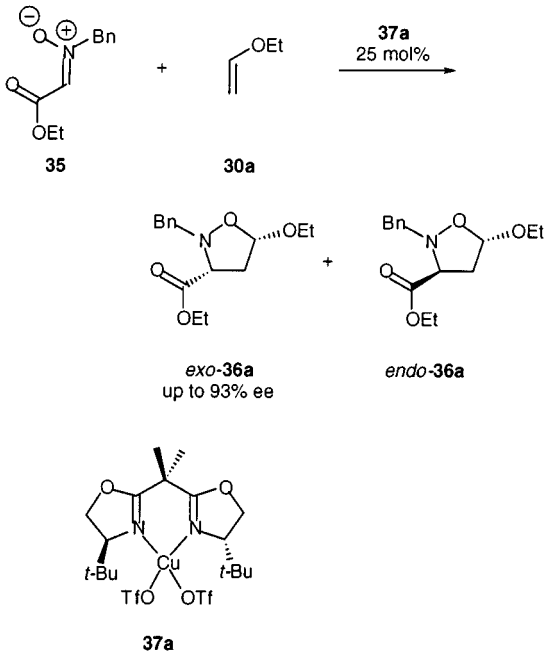
The polymeric ligand's monomeric counterpart **28g** was also synthesised and applied in the 1,3-dipolar cycloaddition reaction in order to compare the properties with the polymeric ligand (Scheme 17). When **28g** in combination with $AlMe_3$ (10 mol%) was used as the catalyst for the reactions between nitrones **3a**–**c** and ethyl vinyl ether **30a**, the reactions proceeded to give the pure *exo*-**9** in yields ranging from 76–93%. The enantioselectivities of the reactions were very high at 94–99% ee, and were thus comparable to the results obtained using the polymeric ligand.



Scheme 17

Copper catalysts

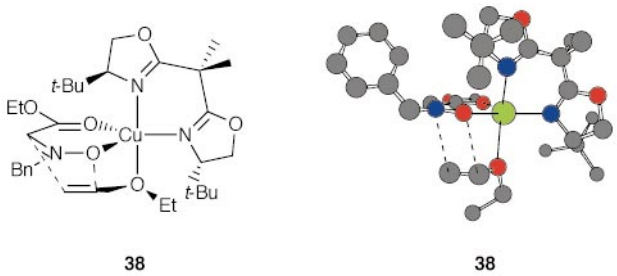
In order to control the stereochemistry in the 1,3-dipolar cycloaddition reactions the bidentate glyoxylate derived nitrone **35**, chiral copper catalysts were applied.[52] For the reaction of nitrone **35**, the electron-rich ethyl vinyl ether **30a** was chosen as the dipolarophile (Scheme 18). A series of chiral catalysts was investigated for the reaction and the $Cu(OTf)_2$–*t*-Bu-BOX complex **37a** was found to be the most suitable catalyst for this reaction. In the presence of 25 mol% of **37a** the reaction proceeded to give a conversion of 98%, an *exo*:*endo* ratio of 84:16, and as the most significant result, *exo*-**36a** was obtained with 89% ee. By changing the solvent to toluene the



Scheme 18

diastereoselectivity of the reaction was slightly lowered, but the enantioselectivity was improved to 93% ee.[52]

In order to account for the stereoselectivity observed in this reaction a model **38** for the intermediate consisting of substrates

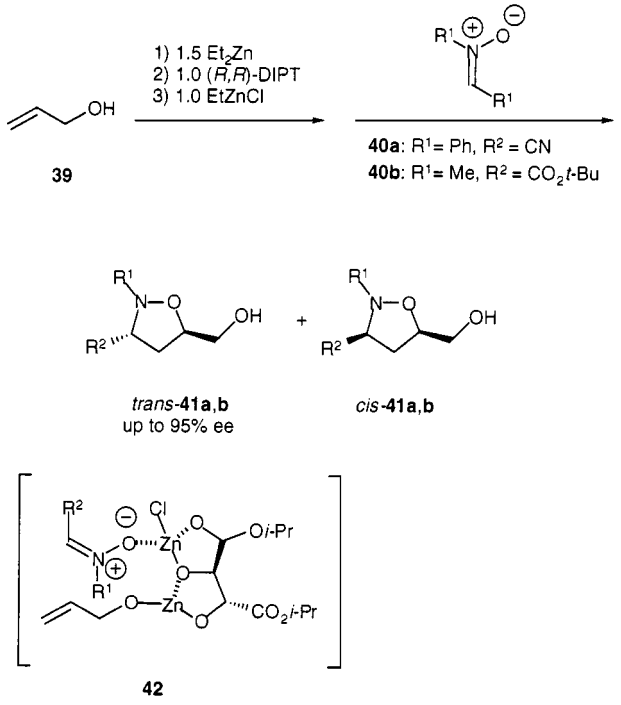


35 and ethyl vinyl ether **30a** coordinated to catalyst **37a** was proposed.[52] In the model the two triflate ligands are dissociated from copper and the ligands are arranged around the copper center as a trigonal bipyramid. It should be noted that in model **38** the oxygen atom of vinyl ether **30a** also coordinates to the metal center. However, a tetrahedral intermediate consisting of only the catalyst and the nitrone could also account for the absolute stereoselectivity of the reaction.

It should also be mentioned that Bosnich *et al.* have applied a chiral titanocene derived catalyst for the inverse electron-demand 1,3-dipolar cycloaddition reaction of nitrones with ketene acetals, however, the highest chiral induction was 14% ee.[53]

Other types of asymmetric catalysis

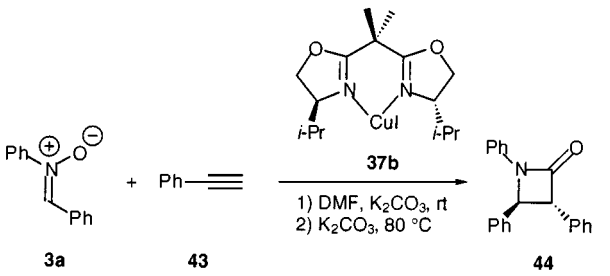
A different catalytic enantioselective approach was developed for the 1,3-dipolar cycloaddition reaction of nitrones with allyl alcohol (Scheme 19).[54] The zinc catalyst complex, which was used in a stoichiometric amount, was generated from allyl alcohol **39**, Et_2Zn, (*R*,*R*)-diisopropyltartrate (DIPT) and EtZnCl. Addition of the nitrone **40a** led to primarily *trans*-**41a**, which was obtained in a moderate yield, however, with a high ee of up to 95%. Application of **40b** as the nitrone in the reaction led to higher yields of **41b** (47–68%), high *trans*-selectivities and up to 93% ee. Compared to other asymmetric metal catalysed 1,3-dipolar cycloaddition reactions of nitrones, this reaction cannot be assigned as normal or inverse electron-demand. The reaction is controlled, rather than by altered FMO energies, instead by the chelation of the substrates to the catalyst



Scheme 19

leading to a favorable entropy of the proposed pseudo-intramolecular intermediate **42**.

Another quite different asymmetric copper catalysed reaction was published by Miura *et al*. in 1995.[55] The reaction of nitrone **3a** and phenylacetylene **43** is catalysed by CuI–*i*-Pr-BOX **37b** as outlined in Scheme 20. The product of this reaction is not a



Scheme 20

1,3-dipolar cycloaddition adduct, rather it is the azetidone **44**. The reaction proceeds, however, *via* an isoxazoline intermediate and is therefore mentioned here. By using 1 equivalent of the catalyst **37b**, the *trans*-isomer **44** is obtained in 54% yield and with 68% ee. If the catalyst loading is lowered to 10 mol% CuI and 20 mol% ligand the selectivity decreases to 57% ee.

Summary

The catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones has reached a mature stage and there are several examples of reactions that proceed with very high enantioselectivities. For the normal electron-demand 1,3-dipolar cycloaddition reaction of nitrones with electron-deficient alkenes a number of metal complexes have been applied successfully. All of these have in common that they favor a bidentate coordination of the alkenoyloxazolidinone (or succinimide) to the metal catalyst. Most of these reactions proceeded with *endo*-selectivity. The chiral $Ni(ClO_4)_2$–DBFOX/Ph has been the most selective catalyst for the *endo*-selective normal electron-demand 1,3-dipolar cycloaddition reaction so far. Application of 1–10 mol% of this catalyst induced in general very high enantioselectivities of up to 99% ee. It has been more difficult to obtain the *exo*-isomer in the above described reaction. The application of succinimide as an auxiliary for the alkene in the $TiCl_2$–TADDOLate catalysed reaction has been the only entry to a highly *exo*-selective reaction and in this case up to 72% ee of the *exo*-isomer was obtained.

Other types of catalysts had to be applied for the inverse electron-demand 1,3-dipolar cycloaddition reaction of nitrones with electron-rich alkenes. Fair enantioselectivities of up to 79% ee were obtained with oxazaborolidinone catalysts. However, the AlMe–3,3′-Ar-BINOLate complexes proved to be superior for reactions of acyclic nitrones and more than > 99% ee has been obtained in some reactions. The CuX_2–BOX catalyst was efficient for reactions of the glyoxylate derived nitrones with vinyl ethers and enantioselectivities of up to 93% ee were obtained. A few examples of different approaches to catalyst induced control of the stereoselectivity of the reaction have also been reported, however, in these examples a stoichiometric amount of the chiral catalyst was required.

The development of catalytic enantioselective 1,3-dipolar cycloaddition is probably going to continue during the next decade and there are some problems that need to be solved. One of the major drawbacks for most of the reactions is the high catalyst loadings that are required. Another challenge is to explore new substrates that are more suitable for application in synthesis. Hopefully, some of these problems will be solved, because the catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones is a highly valuable reaction for the control of multiple stereocenters in a single reaction step.

Acknowledgements

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