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Chiral DBFOX/Ph Complex Catalyzed Enantioselective Nitrone Cycloadditions to α,β-Unsaturated Aldehydes

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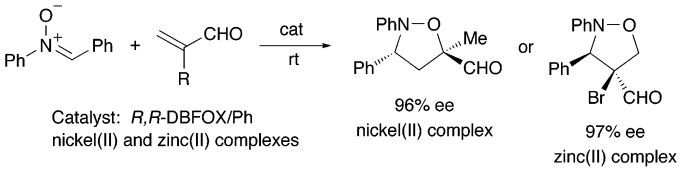
ABSTRACT



1,3-Dipolar cycloadditions of nitrones with α-alkyl- and α-arylacroleins are catalyzed with the DBFOX/Ph complexes of nickel(II) and magnesium(II) salts to produce the sterically controlled isoxazolidine-5-carbaldehydes, while the reactions with α-bromoacrolein are effectively catalyzed with the zinc(II) complexes to produce the electronically controlled isoxazolidine-4-carbaldehydes. Enantioselectivities up to 99.5% ee have been observed in the reactions performed at room temperature.

Catalyzed enantioselective 1,3-dipolar cycloadditions of nitrones provide a direct synthetic access to enantiomers of isoxazolidines whose high synthetic potential is based on their transformations to γ-amino alcohols through reductive cleavage of the nitrogen−oxygen bond.[1] Although various chiral Lewis acids have been successfully applied to make isoxazolidines through nitrone cycloadditions,[2,3] the nickel(II) or iron(II) chiral complexes derived from DBFOX/Ph ligand[3] and the nickel(II) complexes derived from Pybox[2i] are among those that thus far provide the best results. Strong binding of nitrones to the catalyst is a serious problem in the Lewis acid catalyzed nitrone cycloadditions, and therefore, bidentate dipolarophiles such as 3-(2-alkenoyl)-2-oxazolidinones have been mostly used to secure the tight coordination of acceptors to the catalyst.[2,3] Successful use of monodentate dipolarophiles in the metal complex catalyzed nitrone cycloadditions has remained relatively unexplored,[4−6] while a few examples of the chiral amine

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(1) For recent reviews, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449−1458. (c) Gothelf, K. V.; Jørgensen, K. A. Asymmetric Reactions. In *Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W., Eds.; John Wiley & Sons: New York, 2002; Chapter 12, pp 817−899.

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(6) (a) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457−2460. (b) Ohtsuki, N.; Kezuka, S.; Kogami, Y.; Mita, T.; Ashizawa, T.; Ikeno, T.; Yamada, T. *Synthesis* **2003**, *9*, 1462−1466.

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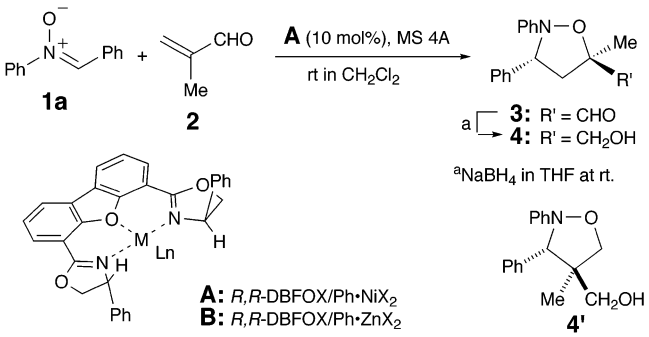
catalyzed nitrone cycloadditions have been reported.[7,8] Therefore, catalyzed enantioselective nitrone cycloadditions to α,β-unsaturated aldehydes are still a challenging research subject.

We have recently reported that a pinhole catalyst effectively activates nitrone cycloadditions to α,β-unsaturated aldehydes and ketones.[4] Nitrones should coordinate predominantly to the catalyst in Lewis acid-catalyzed nitrone cycloadditions.[9] However, if the resulting Lewis acid/nitrone complexes still have a catalytic capability, the complexes would work as chiral pinhole catalysts (Scheme 1, **A** and **B**,

Scheme 1

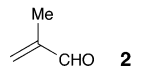
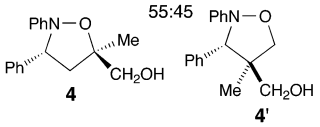
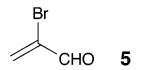
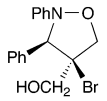
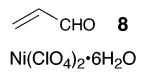
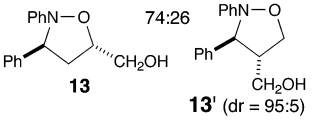
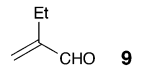
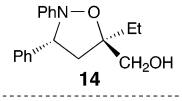
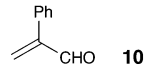
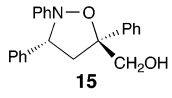
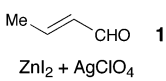
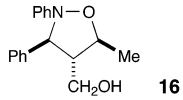
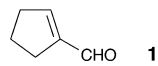
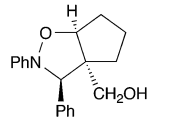


Ln = nitrone(s) and/or anionic counterion(s)) and effective activation of α,β-unsaturated aldehydes can be expected. This expectation has actually been realized.

In this paper, we describe the DBFOX/Ph complex catalyzed enantioselective nitrone reactions to α,β-unsaturated aldehydes. The sterically controlled isoxazolidine-5-carbaldehydes are produced in the reactions of α-alkyl- and α-arylacroleins in the presence of either nickel(II) or magnesium complexes, while the electronically controlled isoxazolidine-4-carbaldehydes are given in the zinc(II) complex-catalyzed reactions with α-bromoacrolein. The reactions with other aldehydes such as acrolein, crotonealdehyde, and 1-cyclopentenecarbaldehyde have been examined under the catalysis of nickel(II), zinc(II), and cobalt(II) complexes. It has been found that a variety of DBFOX/Ph complexes of zinc(II) salts are isolable and storable in open air without loss of catalytic activity, and replacement of one iodide anion of the ZnI_2 complex with a noncoordinating anion leads to the most powerful catalysts. Enantioselectivities up to 99.5% ee have been observed in the reactions performed at room temperature.

Reaction of *N*-benzylideneaniline *N*-oxide (**1a**) with methacrolein (**2**) in dichloromethane at room temperature (48 h) in the presence of MS 4A (500 mg/mmol) and 10 mol % of the nickel(II) complex **A**, prepared by stirring equivalents of *R*,*R*-DBFOX/Ph and $Ni(ClO_4)_2 \cdot 6H_2O$ in the same solvent for a few hours, gave a single diastereomer of isoxazolidine-5-carbaldehyde **3** as a sterically controlled regioisomer as shown in Scheme 1.[10] Reduction of **3** with $NaBH_4$ produced isoxazolidine-5-methanol **4** (73% based on **1a**) whose enantiopurity was determined to be 96% ee.[11,12] Although the zinc(II) complex catalyst **B** (X = ClO_4) was more active than the nickel(II) complex **A**, the product obtained after the reduction of **3** with $NaBH_4$ was a 55:45 regioisomeric mixture of **4** (95% ee) and **4′** (83% ee) as shown in Table 1.

Table 1. Enantioselective Nitrone Cycloadditions to α,β-Unsaturated Aldehydes[a]

aldehyde	conditions and results[b]	products[c]
 **2**	1) rt, 48 h 73% 96% ee 2) rt, 4 h 98% rs = 55:45 95 / 83% ee	 55:45 **4** **4'**
 **5** $ZnI_2 + 2AgClO_4$	rt, 3 h 85% ds = 95:5 98 / 89 %ee	 **7a**
 **8** $Ni(ClO_4)_2 \cdot 6H_2O$	-10 °C, 72 h 75% rs = 74:26 98 / 91% ee	 74:26 **13** **13'** (dr = 95:5)
 **9** $Ni(ClO_4)_2 \cdot 6H_2O$	rt, 48 h 98% rs = 98:2 77 / 55 %ee	 **14**
 **10** 1) $Ni(ClO_4)_2 \cdot 6H_2O$ 2) $Mg(ClO_4)_2$	1) rt, 22 h quant 80% ee 2) rt, 22 h quant 78% ee	 **15**
 **11** $ZnI_2 + AgClO_4$	rt, 69 h 78% ds = 80:20 49 / 84% ee	 **16**
 **12** $Co(ClO_4)_2 \cdot 6H_2O$	rt, 24 h 46% 92% ee	 **17**

[a] In room temperature in dichloromethane in the presence of 10 mol % of the DBFOXPh complex catalyst and MS 4A. [b] rs: regioselectivity. ds: diastereoselectivity. [c] Products were obtained by reduction of the cycloadducts with sodium borohydride in ethanol.

Thus, the zinc complex **B** tends to activate the formation of electronically controlled cycloadduct **4′**. In our previous theoretical work on Lewis acid catalyzed nitrone cycloadditions,[9] a stronger Lewis acid favors the preferred formation of electronically controlled cycloadducts.

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(9) Tanaka, J.; Kanemasa, S. *Tetrahedron* **2001**, *57*, 899−905.

(10) General experimental procedures have been described in the Supporting Information for the reactions between nitrone **1a** and methacrolein (**2**) as well as between **1a** and α-bromoacrolein (**5**).

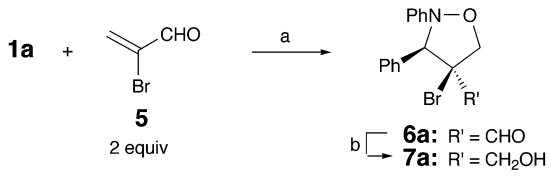
(11) In the reactions of **1a** to **2** and **5**, chemical yields and regio- and diastereoselectivities are given for isoxazolidinecarbaldehydes **3** and **6**, while enantioselectivities are given for isoxazolidinemethanols **4** and **7**.

(12) Enantioselectivities have been determined on the basis of the chiral hplc analysis (Daicel Chiral Cell OD-H) for isoxazolidine methanols **4** and **7**.

1,3-Dipolar cycloadditions of nitrone **1a** with a variety of α,β-unsaturated aldehydes were examined, and the results are listed in Table 1. In all cases of nitrone cycloadditions to α,β-unsaturated aldehydes, the use of MS 4A was essential in order to attain high reactivity and selectivities. For example, reaction of **1a** with **5** catalyzed by the zinc(II) complex **B** (X = OTf) at −40 °C in the absence of MS 4A resulted in much lower chemical yields and selectivities (46 h, 36%, endo/exo = 87:13 for **6a**, 86% ee for **7a**). Accordingly, all the reactions shown in Table 1 have been performed in the presence of MS 4A (500 mg/mmol).

The nitrone cycloaddition of **1a** with α-bromoacrolein (**5**), which is more electrophilic than **2**, is sluggish under uncatalyzed conditions, and the electronically controlled isoxazolidine-4-carbaldehyde regioisomer **6a** was given as a 51:49 diastereoisomeric mixture only in a poor yield (41 h, 23%). Switch of the regioselectivity observed is dipolarophile-controlled due to the strongly electron-withdrawing nature of α-bromide moiety of **5**. The nickel(II) complex catalyst **A** (X = ClO_4) was not effective to activate this reaction showing poor catalytic activation and enantioselectivity (31% after 41 h at room temperature, endo/exo = 90:10, 42% ee for the major *endo*-**6a**). However, we have found that the zinc(II) complex **B** is the most effective catalyst. Thus, the catalyzed reaction was completed in 1 h at room temperature in the presence of the zinc(II) complex **B** (X = OTf, 10 mol %)[13] and MS 4A, producing a 95:5 diastereomeric mixture of **6a** in 85% yield (Scheme 2).[10−12]

Scheme 2



[a]**B** (10 mol%), $AgClO_4$ (n mol%), MS 4A, rt, CH_2Cl_2. [b]$NaBH_4$ in THF at rt.

	n/mol %	time/h	yield/%	*endo*/*exo*	ee/%
$ZnBr_2$	0	10	65	81/19	16/3
	10	3	90	95/5	94/51
ZnI_2	0	3	72	94/6	95/84
	10	0.5	94	98/2	97/89
	20	6	91	88/12	97/94

Yields and diastereoselectivities are for **6a**, ee/% for **7a**.

Enantioselectivity of the major endo cycloadduct **6a** was determined to be 98% ee after its $NaBH_4$ reduction to isoxazolidine-4-methanol **7a**. Thus, the electronically controlled regioisomer **6a** was the sole product in the reaction of **1a** with **5**, regardless of the presence or absence of catalyst

The reaction of nitrone **1a** with acrolein (**8**) showed a low regioselectivity (rs = 74:26) even under the catalysis of the nickel(II) complex **A** (X = ClO_4), but enantioselectivities were excellent both for regioisomers **13** and **13′**. Reactions to α-ethylacrolein (**9**) and α-phenylacrolein (**10**), having an α-substituent bulkier than that of **2**, were exclusively regioselective in favor of the sterically controlled isoxazolidine-5-methanols **14** and **15**, respectively, under the catalysis of the nickel(II) and magnesium(II) complexes, followed by the sodium borohydride reduction. However, enantioselectivities in these cases were moderate. Crotonaldehyde (**11**) as 1,2-disubstituted alkene was successfully activated with the zinc(II) complex **B** (X_2 = IOTf) to show the exclusive regioselectivity, but both diastereoselectivity and enantioselectivity were low. Although other catalysts failed to activate cyclopentene-1-carbaldehyde (**12**), high enantioselectivity was attained only by catalysis of the cobalt(II) perchlorate complex.

A dramatic difference of catalytic effectiveness was observed depending upon the halide counteranions of the zinc complex catalysts (Scheme 2). Thus, the zinc(II) iodide complex **B** (X = I) effectively activated the reaction of nitrone **1a** with α-bromoacrolein **5** showing excellent selectivities (3 h at room temperature, 72%, endo/exo = 94:6 for **6a**, 95% ee for **7a**). However, to our surprise, the zinc(II) bromide complex **B** (X = Br) gave much lower selectivities (10 h, 65%, endo/exo = 81:19 for **6a**, 16% ee for **7a**). Based on the difference of bond energies between the Zn−I and Zn−Br bonds,[14] we believe that at least one of the iodide anions of complex **B** (X = I) is dissociated from the metal center of the complex under the reaction conditions, while both bromide ions of complex **B** (X = Br) stay on the zinc metal.

When one of the bromide ions of **B** (X = Br) was replaced with a less coordinating perchlorate anion by treatment with 1 equiv of $AgClO_4$, a great improvement of both reactivity and selectivities resulted as shown in Scheme 2 (3 h, 90%, endo/exo = 95:5 for **6a**, 94% ee for **7a**). This indicates that the zinc(II) bromide complex **B** (X = Br), which has only one vacant position on the metal center, shows insufficient catalytic activity in the nitrone cycloadditions with α-bromoacrolein; two vacant positions are essential for both high catalytic activity and selectivity. These observations provide us important information for the consideration of reaction mechanism.

It should be noted that the zinc(II) halide complexes **B** (X = I and Br) were isolable and storable in open air without loss of catalytic activity.[15] Exchange of either one or both of the iodide ions of complex **B** (X = I) with noncoordinating counteranions such as perchlorate, tetrafluoroborate, and triflate ions leads to the corresponding zinc(II) complexes which are more reactive catalysts. All of the resulting complexes were again stable enough to be isolated and stored.[15] Thus, when the catalysts either in situ-prepared or isolated were employed in the reactions of **1a** with **5** and

(13) The DBFOX/Ph complex of zinc(II) triflate was prepared by stirring equimolr amounts of the ligand and $Zn(OTf)_2$ in dichloromethane for a few hours at room temperature. The resulting heterogeneous mixture was used for the subsequent reactions with nitrones.

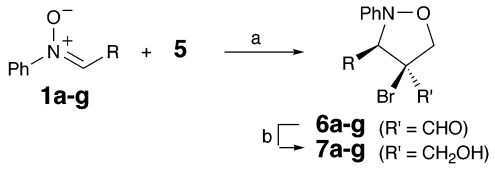
(14) The bond energy for the first ionization of $ZnBr_2$ is much higher than that of ZnI_2 (Liao, M.-S.; Zhang, Q.; Schwarz, W. H. E. *Inorg. Chem.* **1995**, *34*, 5597−5605).

(15) ^{1}H NMR Spectra of the derivative of DBFOX/Ph·ZnX_2 complexes will be reported elsewhere in near future. Shirahase, M.; Kanemasa, S.; Hasegawa, M. Manuscript in preparation.

the catalytic activity was compared, comparable results were observed to confirm the high stability of all these complex catalysts. Especially active were the *R*,*R*-DBFOX/Ph complexes of zinc salts having the formula of $ZnIClO_4$ and $ZnIBF_4$, which can be derived by treatment of the diiodide complex **B** (X = I) with one equivalent amount of silver ions bearing a less coordinating anion. When the reaction temperature was lowered to −40 °C (40 h) either in the reaction catalyzed by the complex derived from **B** (X = I) and $AgClO_4$ (1 equiv, 10 mol %) or that catalyzed by the complex **B** (X = OTf), endo cycloadduct **6a** was produced in 83 or 94% with an enantioselectivity of 99.5 or 99.7% ee for **7a**, respectively.

After optimization, the reactions of nitrones **1a**−**g** having a variety of *C*-substituents with α-bromoacrolein **5** were examined in the presence of a catalytic amount (10 mol %) of the zinc(II) complex **B** (X_2 = $IClO_4$) at room temperature (Scheme 3). In almost all the cases, excellent endo selectivities and enantioselectivities were obtained for isoxazolidine-4-carbaldehydes **6a**−**g** and isoxazolidine-4-methanols **7a**−**g**. In particular, *N*-(2-naphthylmethylene)aniline *N*-oxide (**1g**) produced the isoxazolidine-4-methanol derivative **7g** in an absolutely high enantioselectivity of 99.5% ee in the reaction performed at room temperature. Such high generality of *C*-substituents of nitrones **1** in the reactions to **5** is also a synthetic advantage of our enantioselective nitrone cycloadditions.

Scheme 3



[a] *R*,*R*-DBFOX/Ph•ZnI_2, $AgClO_4$ (10 mol% each), MS 4A (500 mg/mmol) in CH_2Cl_2, rt. [b] $NaBH_4$ in THF at rt.

R		time/h	yield/%	ds	ee/%(major)
Ph	**a**	0.5	94	98/2	97
4-MeC_6H_4	**b**	1	96	98/2	97
4-BrC_6H_4	**c**	0.5	95	91/9	97
4-$NO_2C_6H_4$	**d**	2	97	>99/1	>99
2-Furyl	**e**	18	76	91/9	90
1-Naph	**f**	1	98	98/2	88
2-Naph	**g**	1	97	90/10	99.5

Yields and diastereoselectivities are for **6**, ee/% for **7**.

The absolute configurations of **3** and **6a** were determined to be the 3*R*,5*R*- and 3*R*,4*R*-enantiomers on the basis of X-ray crystal structures of the *p*-bromobenzoate derivatives **18** and **19** of isoxazolidine methanols **4** and **7a**, respectively.[16] This indicates that the preferred attack of nitrones to the Re(α)-faces of α,*β*-unsaturated aldehydes **2** and **5** took place in the transition structure of these nitrone cycloadditions. The absolute configurations of **14** and **15** were temporarily assigned as shown in Table 1 on the basis of the expected structural similarity of **9** and **10** to the starting material **2**. Absolute configuration of the cycloadduct **17** to cyclopentene-1-carbaldehyde (**12**) was detremined to be 3*R*,3a*S*,6a*S*-enantiomer by comparison of its optical rotation of the authentic sample.[5b] Other cycloadducts **13** and **16** derived from **8** and **11**, respectively, remained uncharacterized.

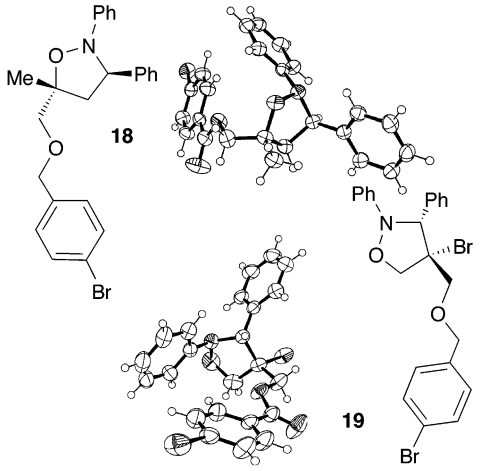


Figure 1. Absolute configurations of derivatives of isoxazolidine-5-methanol **18** and -4-methanol **19**.

In conclusion, nitrone cycloadditions to a variety of α,*β*-unsaturated aldehydes were effectively catalyzed by the nickel(II), zinc(II), magnesium(II), and cobalt(II) complexes derived from the *R*,*R*-DBFOX/Ph ligand. Highly useful were the nickel(II) and magnesium(II) complexes for the reactions of methacrolein, and the zinc(II) complexes for the reactions of α-bromoacrolein. Especially active are the catalysts derived from the ZnI_2 complex by replacement of an iodide anion with a noncoordinating anionic ligand. The highest enantioselectivity up to 99.5% ee was observed in the reaction with α-bromoacrolein performed at room temperature. Other α-substituted acrolein derivatives as well as 1-cyclopentenecarbaldehyde were also effectively catalyzed. Thus, the reactions of acyclic nitrones with α,*β*-unsaturated aldehydes, catalyzed by DBFOX/Ph complexes, provided much higher enantioselectivities than the reported examples.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds as well as X-ray crystallographic data of *p*-bromobenzoates of **4** and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) X-ray analysis data for **18** and **19** are given in the Supporting Information.