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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 4061–4063

Improved catalysis of nitrone 1,3-dipolar cycloadditions by solving the aggregation issue of the DBFOX/Ph-transition metal complexes

Moto Shirahase,[b] Shuji Kanemasa[a,*] and Masayuki Hasegawa[b]

[a]*Institute for Materials Chemistry and Engineering, CREST of JST (Japan Science and Technology Agency), Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan*
[b]*Department of Molecular and Material Sciences, Graduate School of Engineering Sciences, Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan*

Received 27 January 2004; revised 25 March 2004; accepted 26 March 2004

Abstract—A new method has been demonstrated to solve the aggregation issue of metal complex catalysts; Steric protection of the metal center of catalysts was effective in the cases of DBFOX/Ph-transition metal complexes by structural modification of chiral ligand. The new ligands have been successfully applied to the nitrone cycloadditions to a variety of α,β-unsaturated aldehydes. Excellent enantioselectivities up to 99% ee have been demonstrated in the reactions at room temperature with a catalytic loading of 2 mol %.

Although some successful examples have been reported for the catalyzed enantioselective nitrone cycloaddition reactions with α,β-unsaturated aldehydes, DBFOX/Ph-transition metal complexes are regarded to be the most useful catalysts.[1,2] In the preceding communication,[1] we have already reported that the complex derived from DBFOX/Ph and zinc(II) triflate, regardless of its extremely small solubility in dichloromethane, works as a powerful catalyst in the enantioselective nitrone cycloadditions with α-bromoacrolein. In general, solubility of metal complexes becomes low when strong attractive interactions work among complex molecules, and the resulting tight aggregation causes the decreased catalytic activity. Therefore, much more efficient catalysis can be expected if the above negative aggregation issue is solved. Steric protection of the metal center of complexes would be one of the most effective solutions. In this communication, we have demonstrated steric protection of the metal center based on the structural modification of DBFOX/Ph ligand. Excellent enantioselectivities of up to 99% were demonstrated in the nitrone cycloadditions to α,β-unsaturated aldehydes at room temperature.

As described above, treatment of DBFOX/Ph ligand **A** with $Zn(OTf)_2$ in dichloromethane (10 mol % each) led to a densely heterogeneous solution,[3] but the resulting suspension successfully catalyzed the reaction of *N*-benzylideneaniline *N*-oxide (**1a**) to α-bromoacrolein (**2**). The cycloadduct **3a**, obtained in 85% yield as the far major diastereomer, was converted into isoxazolidine-4-methanol **4a**, whose enantioselectivity was determined to be 97% ee. In the preparation step of the DBFOX/Ph-zinc complex catalyst, the insoluble materials were all filtered off and then the filtrate was evaporated.[4] ^{1}H NMR analysis of the residue obtained showed that the free DBFOX/Ph ligand **A** used was almost quantitatively recovered, indicating that the complex formation was difficult due to the extremely small solubility of $Zn(OTf)_2$ in dichloromethane.[5,6] Addition of nitrone **1a** to this suspension did not improve the solubility at all. Thus, the chiral catalyst **A** ($MX_2 = Zn(OTf)_2$) should be highly active in the nitrone cycloadditions to **5** if this is formed in a higher concentration.

Coplanarity of the heterocyclic rings of ligand **A** may be a major reason for the easy aggregation, and therefore for the decreased solubility of the complexes.

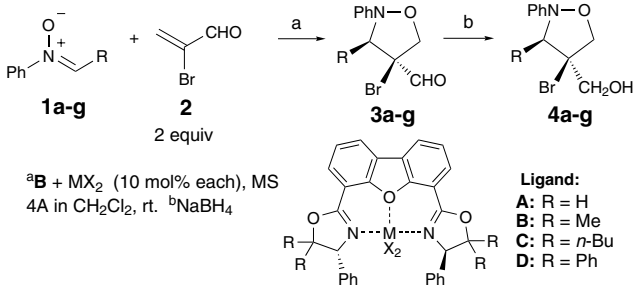
Keywords: Nitrone; 1,3-Dipolar cycloaddition; Aldehyde dipolarophile; Catalyzed enantioselective reaction.
* Corresponding author. Tel.: +81-9258-37802; fax: +81-9258-37875; e-mail: kanemasa@cm.kyushu-u.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.151

Introduction of substituents at the 5-positions of the oxazoline rings of **A** would suppress the undesired aggregation and improved catalytic activity is expected. Substituted DBFOX/Ph derivatives, called the second generation of DBFOX/Ph series, were synthesized via straightforward synthetic routes; the starting methyl phenylglycinate was converted into β-amino tertiary alcohols by treating with excess Grignard reagents, and the resulting alcohols were converted into the substituted DBFOX/Ph derivatives according to the usual synthetic route to bisoxazolines.[7]

When the tetramethyl-substituted ligand **B** was treated with $Zn(OTf)_2$ under stirring in dichloromethane, a clear solution resulted within a few minutes. The complex formation was definitely confirmed by a ^1H NMR spectral study.[8,9] Other metal salts could also be successfully applied to prepare the corresponding complexes of **B** and these were effectively used in the cycloadditions of **1a** to α-bromoacrolein **2** (Scheme 1). Except for the complexes of **B** derived from $Ni(ClO_4)_2{\cdot}6H_2O$ and $ZnBr_2$, those derived from metal salts such as $Co(ClO_4)_2{\cdot}6H_2O$, $Co(BF_4)_2$, $Zn(ClO_4)_2$, and $Zn(OTf)_2$ were all highly effective catalysts when applied to the reactions at room temperature in the presence of 10 mol% of the catalyst. Especially, it should be emphasized that *endo*-selectivities were exclusively high in all cases.

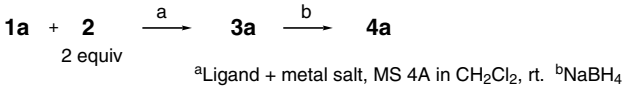
Other nitrones **1b–g** having several aryl substituents on the nitrone carbon atom were examined in the 1,3-dipolar cycloaddition reactions with α-bromoacrolein **2** in the presence of 10 mol% of complex of **B** ($MX_2 = Zn(OTf)_2$) to give cycloadducts **3b–g** with exclusive enantioselectivity and *endo*-selectivity (Scheme 1). The highest enantioselectivity of 99.9% ee was observed with the exclusive *endo*-selectivity in the reaction with *N*-(4-nitrobenzylidene)aniline *N*-oxide (**1d**).



Compd	R	Metal salt	Time/h	Yield/%[a]	ds	ee %[b]
a	Ph	$Ni(ClO_4)_2{\cdot}6H_2O$	4.5	59	94/6	18/-1
a	Ph	$Co(ClO_4)_2{\cdot}6H_2O$	2	90	99/1	95/-
a	Ph	$Co(BF_4)_2{\cdot}6H_2O$	1	92	>99/1	98
a	Ph	$ZnBr_2$	20	73	85/15	26/9
a	Ph	ZnI_2	1.5	98	>99/1	99
a	Ph	$Zn(ClO_4)_2$	0.75	96	99/1	99/69
a	Ph	$Zn(OTf)_2$	2	quant	>99/1	97/-
b	4-MeC_6H_4	$Zn(OTf)_2$	1	94	99:1	94
c	4-BrC_6H_4	$Zn(OTf)_2$	1	89	>99/1	98
d	4-$NO_2C_6H_4$	$Zn(OTf)_2$	2	88	>99/1	>99
e	2-Furyl	$Zn(OTf)_2$	20	67	95:5	97
f	1-Naphthyl	$Zn(OTf)_2$	1	98	>99/1	>99
g	2-Naphthyl	$Zn(OTf)_2$	1	96	>99/1	98

[b]Determined for **4** by a chiral HPLC (Daisel Chiral cell OD-H). [a]Yield of **3**

Scheme 1.



Ligand (mol%)	Temp/°C	Time/h[c]	Yield/% **3a**	ds	ee %[d] **4a**
A + $Zn(OTf)_2$					
2	rt	21	58	86/14	23/12
2	rt	1 (SA)	37	86/14	78/43
2	rt	1 (SA)	59	91/9	92/25
B + $Zn(OTf)_2$					
2	rt	17.5	61	84/16	57/3
2	rt	1 (SA)	73	98/2	97/4
1	-20	91 (SA, 10)	41	96/4	95/26
C + $Zn(OTf)_2$					
2	rt	1 (SA)	68	99/1	96/-

[c]SA: slow addition of nitrone **1a** in the period of time shown
[d]Determined by a chiral HPLC (Daisel Chiral cell OD-H).

Scheme 2.

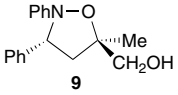
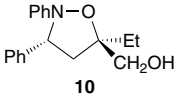
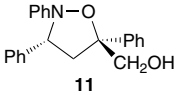
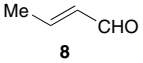
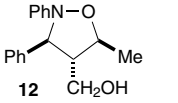
When the catalytic loading was reduced to 2 mol% for **1a**, the reaction catalyzed by the complex of **B** ($MX_2 = Zn(OTf)_2$) became rather slow giving a lowered enantioselectivity of 57% ee (Scheme 2). However, the reaction was completed within 1 h under SA conditions[10] at room temperature giving **3a** in 73% yield with an enantioselectivity of 97% ee for **4a**. Even with the decreased catalytic loading of 1 mol%, an excellent enantioselectivity of 95% ee was achieved. The complex derived from tetrabutyl-DBFOX/Ph **C** and $Zn(OTf)_2$ showed a catalytic activity similar to that of **B**, while the complex of tetraphenyl-DBFOX/Ph **D** was much less active.[11] Thus, highly efficient catalytic activity of the complexes derived from the second generation of DBFOX/Ph ligands **B** and **C** is clear (Scheme 2).

Combination of the second generation of DBFOX/Ph ligand with nickel(II) salts was also effective. Thus, the reaction of **1a** with methacrolein (**5**) in the presence of 10 mol% of the complex of **B** ($MX_2 = Ni(ClO_4)_2{\cdot}nH_2O$) gave isoxazolidine-5-methanol **9** as a single product in 98% yield (*endo* only, 99% ee, Table 1). Even a catalytic loading of 2 mol% worked well at 0 °C giving *endo*-**9** in an excellent enantioselectivity of 96% ee, while the reaction catalyzed by complex of **A** ($MX_2 = Ni(ClO_4)_2{\cdot}nH_2O$, 2 mol%) provided a relatively low enantioselectivity of 75% ee.

The cycloadditions of **1a** with both α-ethylacrolein (**6**) and α-phenylacrolein (**7**), in the presence of the nickel (II) complex of **C** ($MX_2 = Ni(ClO_4)_2{\cdot}nH_2O$, 10 mol%), were highly enantioselective producing **10** (quant, *endo* only, 92% ee) and **11** (53%, *endo* only, 95% ee), respectively. Although enantioselectivity was not very high (77% ee for **12**), the reaction of **1a** with crotonaldehyde (**8**) was almost exclusively *endo*-selective in the presence of the zinc(II) complex of **B** ($MX_2 = Zn(OTf)_2$, 10 mol%).

In conclusion, we have successfully solved the aggregation issue of the DBFOX/Ph-transition metal complexes

Table 1. Enantioselective nitrone cycloadditions to α,β-unsaturated aldehydes **5**–**8**[a]

Aldehyde	Conditions and results	Products[b]
 **5**	**B**+$Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol%), rt, 22 h, 98%, single, 99% ee **B**+$Ni(ClO_4)_2{\cdot}6H_2O$ (2 mol%), 0 °C, 48 h, 91%, single, 96% ee	 **9**
 **6**	**B**+$Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol%), rt, 29 h, quant, single, 92% ee	 **10**
 **7**	**B**+$Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol%), rt, 24 h, 67%, single, 84% ee	 **11**
 **8**	**B**+$Zn(OTf)_2$ (10 mol%), rt, 14 h, SA, 74%, 99:1, 77% ee	 **12**

[a] All the reactions were performed in dichloromethane in the presence of the complexes of **B** and MS 4 A.

[b] Products **9**–**12** were obtained by reduction of the cycloadducts with sodiumborohydride in ethanol.

by structural modification of the chiral ligand DBFOX/Ph. These new chiral ligands, named as the second generation of DBFOX/Ph series, worked well to improve catalysis in the nitrone cycloadditions using a variety of α,β-unsaturated aldehyde dipolarophiles. Excellent enantioselectivities up to 99% ee have been demonstrated with a catalytic loading of 2 mol%.

Acknowledgements

A financial support from the Grant-in-Aid for Scientific Research on Priority Areas (A) (No 13029087) from the Ministry of Education, Culture, Sports, Science, and Technology of Japanese Government is acknowledged.

References and notes

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2. (a) Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968–4969; (b) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457–2460; (c) Ohtsuki, N.; Kezuka, S.; Kogami, Y.; Mita, T.; Ashizawa, T.; Ikeno, T.; Yamada, T. *Synthesis* **2003**, *9*, 1462–1466; (d) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodríguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716–2717.
3. The colorless suspension remained all the time until the reaction mixture was quenched with saturated ammonium chloride after the completion of reaction.
4. General procedure for the preparation of DBFOX/Ph complexes is as follows: Equimolar amounts of DBFOX/Ph and a metal salt are stirred in dichloromethane for a few hours at room temperature, and a clear solution including the resulting complex is evaporated in vacuo to give a solid of the complex.
5. We have confirmed, on the basis of the experiment by use of a reference compound, that the DBFOX/Ph ligand used for the complex preparation experiment was recovered almost quantitatively without formation of complex.
6. A variety of the DBFOX/Ph complexes of other zinc(II) salts could be isolated and they were easily characterized by ^1H NMR spectra.
7. (a) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074–3088; (b) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417–2428.
8. Complexes of **B**–**D** (M = $Zn(OTf)_2$) were isolable and could be stored in open air for months without loss of catalytic activity.
9. A solution of equimolar amounts of ligand **B** and $Zn(OTf)_2$ in dichloromethane was stirred at room temperature in a few minutes and the solvent was evaporated in vacuo. The residue was dissolved in deuteriochloroform, and the solution was submitted to ^1H NMR analysis showing quantitative formation of the complex.
10. See the footnote "a" in the table included in Scheme 2.
11. Complexes derived from **D** show much smaller solubility in dichloromethane than the complexes of other ligands **A**–**C**.