Highly Endo- and Enantioselective Asymmetric Nitrone Cycloadditions Catalyzed by the Aqua Complex of 4,6-Dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)−Nickel(II) Perchlorate. Transition Structure Based on Dramatic Effect of MS 4A on Selectivities

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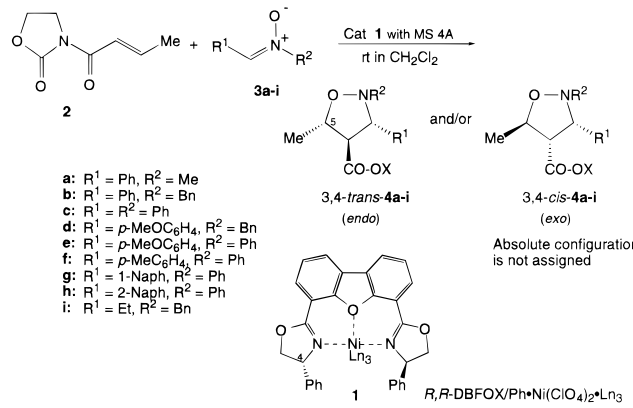
Received June 29, 1998

1,3-Dipolar cycloaddition to alkene dipolarophiles is now the most useful method to make many stereochemically defined five-membered heterocycles.[1] Although a variety of diastereoselective 1,3-dipolar cycloadditions have been developed, enantioselective versions are still limited.[2] Nitrones[3] are important 1,3-dipoles that have been the target of catalyzed enantioselective reactions. Three different approaches to catalyzed enantioselective reactions have been taken: (1) activation of electron-deficient alkenes by a chiral Lewis acid,[4−8] (2) activation of nitrones in the reaction with ketene acetals,[9] and (3) coordination of both nitrones and allylic alcohols on a chiral catalyst.[10] Among these approaches, the dipole/HOMO controlled reactions of electron-deficient alkenes such as *N*-alkenoyl-2-oxazolidinones or *N*-alkenoylsuccinimides[4b] are especially promising because a variety of combinations between chiral Lewis acids and electron-deficient alkenes have been investigated in the study of catalyzed enantioselective Diels−Alder reactions. Enantioselectivities in catalyzed nitrone cycloadditions sometimes exceed 90% ee, but the efficiency of catalytic loading remains insufficient.

In the present communication, we report asymmetric 1,3-dipolar cycloadditions of nitrones to 3-(2-alkenoyl)-2-oxazolidinones catalyzed by the aqua complex derived from (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) ligand (*R*,*R*-DBFOX/Ph)[11] and $Ni(ClO_4)_2 \cdot 6H_2O$.

In the presence of 10 mol % of the anhydrous nickel catalyst **1** (Ln = none),[12] which can be prepared in situ from (*R*,*R*)-DBFOX/Ph ligand, $NiBr_2$, and two equimolar amounts of AgClO$_4$,[13] the reaction of 3-crotonoyl-2-oxazolidinone (**2a**) with *N*-benzylidenemethylamine *N*-oxide (**3a**) produces 3,4-*trans*-isoxazolidine **4a** in near perfect endo selectivity (endo:exo = 99:1) and enantioselectivity for the 3*S*,4*R*,5*S* enantiomer (>99% ee for the endo isomer, Scheme 1 and Table 1, entry 1). The aqua nickel complex **1** (Ln = H_2O), which can be simply prepared in situ by stirring equimolar amounts of the (*R*,*R*)-DBFOX/Ph ligand and $Ni(ClO_4)_2 \cdot 6H_2O$ in dichloromethane for a few hours, gives a comparable result in a similar reaction in the presence of MS 4A (entry 2). The simple preparation procedure of the aqua catalyst should be attractive.

Scheme 1



The presence of MS 4A is essential to attain high selectivities, especially in the reactions catalyzed by the aqua complex. In the absence of MS 4A, the endo selectivity and enantioselectivity for 3,4-*trans*-isoxazolidines are both lowered.[14] Jørgensen was the first to observe a dramatic effect of MS 4A in Lewis acid-catalyzed nitrone cycloadditions.[5] In his reaction, the chemical yield of the cycloadduct was not affected by the absence of MS 4A, but the endo selectivity was lowered (endo:exo, from 92:8 to 65:35) and the enantioselectivity almost disappeared (79 to 2% ee).[15] Our results are comparable. Although the role of MS 4A cannot yet be fully explained,[16] it certainly works as dehydrating agent. In a reaction catalyzed by the aqua nickel complex **1** (Ln = H_2O), anhydrous magnesium sulfate can replace MS 4A, but the reaction becomes a little slower (entry 8).

Reactions of other nitrones **3b**−**f** (entries 3−11) are also diastereoselective (endo:exo ≥ 95:5) and enantioselective for *endo*-**4b**−**f** (higher than 95% ee for **4a**,**b**,**d**,**f** and 89% ee for **4c**,**e**). High efficiency of the catalytic cycle can be demonstrated in the

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(1) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984.

(2) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909.

(3) (a) Breuer, E.; Aurich, H. G.; Nielsen, A. *Nitrones, Nitronates and Nitroxides*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, UK, 1989; Chapters 2 and 3, pp 139−312. (b) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 9, pp 83−168.

(4) (a) Jensen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *Helv. Chim. Acta* **1997**, *80*, 2039−2046. (b) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471−2477. (c) Gothelf, K. V.; Jørgensen, K. A. *Acta Chem. Scand.* **1996**, *50*, 652−660. (d) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59−64. (e) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687−5991.

(5) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346−355. They have recently reported a paper discussing the role of MS 4A: Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483−5488.

(6) Sanchez-Blanco, A. I.; Gothelf, K. V.; Jørgensen, K. A. *Tetrahedron Lett.* **1997**, *38*, 7923−7926.

(7) Hori, K.; Kodama, H.; Ohta, T. Furukawa, I. *Tetrahedron Lett.* **1996**, *37*, 5947−5950.

(8) (a) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840−5841. (b) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997**, 1039−1040.

(9) (a) Seerden, J.-P. G.; Boeren, M. M. M.; Scheeren, H. W. *Tetrahedron* **1997**, *53*, 11843−11852. (b) Seerden, J. P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 4419−4422.

(10) Ukaji, Y.; Taniguchi, K.; Sada, K.; Inomata, K. *Chem. Lett.* **1997**, 547−548.

(11) (a) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 6454−6455. (b) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074−3088.

(12) DBFOX/Ph complexes of iron(II), zinc(II), and magnesium perchlorates show satisfactory selectivities in the reactions of **2** with nitrone **3c** at room temperature in the presence of MS 4A: DBFOX/Ph•$Fe(ClO_4)_2$ (10 mol %) 69%, endo:exo = 95:5, >99% ee for endo isomer; DBFOX/Ph•$Zn(ClO_4)_2$ (10 mol %) 100%, endo:exo = 94:6, 86% ee for endo isomer; DBFOX/Ph•$Mg(ClO_4)_2$ (10 mol %) 100%, endo:exo = 75:25, 86% ee for endo isomer.

(13) Although the resulting AgBr can be removed with the aid of a syringe filter, this filtration procedure is not necessary. Equivalent selectivities result without filtration procedure.

(14) The iron complex catalyzed reaction shown in ref 12 in the absence of MS 4A gives lower selectivities (endo:exo = 68:32, 21% ee for endo isomer *endo*-**4a**).

(15) The reaction of *N*-benzylideneaniline *N*-oxide with 3-crotonoyl-2-oxazolidinone in the presence of catalyst (10 mol %) prepared from isopropylidene-2,2′-bis(4-phenyloxazoline) and MgI_2/I_2 at room temperature for 24 h.

(16) Many examples are known for the effect of MS 4A in Lewis acid-catalyzed asymmetric reactions: (a) Posner, G. H.; Dai, H. Y.; Bull, D. S.; Lee, J. K.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N. *J. Org. Chem.* **1996**, *61*, 671−676. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820 and references therein.

10.1021/ja982254e CCC: $15.00
Published on Web 11/11/1998

Table 1. Nitrone Cycloadditions of 3-Crotonoyl-2-oxazolidinone (**2a**) in the Presence of the DBFOX/Ph·$Ni(ClO_4)_2$ Complexes Leading to Isoxazolidines **4a**−**i**

entry	**3**	catalyst/mol %	MS 4A[a]	temp/°C	time/h	product	yield/%	ds[b]	% ee[c]
1	**3a**	$Ni(ClO_4)_2$/10	100	rt	72	**4a**	63	99:1	>99
2	**3a**	$Ni(ClO_4)_2$·$6H_2O$/10	100	rt	72	**4a**	72	98:2	>99
3	**3b**	$Ni(ClO_4)_2$·$6H_2O$/10	500	rt	48	**4b**	76	>99:1	95
4	**3c**	$Ni(ClO_4)_2$·$6H_2O$/10	300	rt	48	**4c**	96	98:2	89
5	**3d**	$Ni(ClO_4)_2$·$6H_2O$/10	300	rt	48	**4d**	73	>99:1	>99
6	**3d**	$Ni(ClO_4)_2$·$6H_2O$/2	500	rt	96	**4d**	75	>99:1	99
7	**3d**	$Ni(ClO_4)_2$·$6H_2O$/1	300	reflux	36	**4d**	37	>99:1	93
8	**3d**	$Ni(ClO_4)_2$·$6H_2O$/10	500[d]	rt	120	**4d**	100	97:3	99
9	**3e**	$Ni(ClO_4)_2$/10	100	0	96	**4e**	87	95:5	89
10	**3e**	$Ni(ClO_4)_2$·$6H_2O$/10	300	rt	72	**4e**	100	>99:1	87
11	**3f**	$Ni(ClO_4)_2$·$6H_2O$/10	500	rt	36	**4f**	100	99:1	>99
12	**3g**	$Ni(ClO_4)_2$·$6H_2O$/10	500	rt	48	**4g**	25	74:26	9
13	**3h**	$Ni(ClO_4)_2$·$6H_2O$/10	500	rt	48	**4h**	100	99:1	45
14	**3i**	$Ni(ClO_4)_2$·$6H_2O$/10	500	rt	48	**4i**	92	94:6	97

[a] Weight of MS 4A (mg) per 1-mmol scale. [b] Endo/exo ratio. [c] % ee for endo isomers (For conditions of chiral HPLC, see Supporting Information). [d] In the presence of magnesium sulfate instead of MS 4A.

reactions of nitrone **3d**: a 99% ee for *endo*-**4d** is recorded with 2 mol % of the catalyst at room temperature (entry 6) and a 93% ee with 1 mol % even under reflux in dichloromethane (entry 7). The nitrone having a bulky aromatic C-substituent such as *N*-(1-naphthylmethylene)aniline *N*-oxide (**3g**) shows a decreased reactivity, the chemical yield, diastereoselectivity, and enantioselectivity being all poor (entry 12), while the isomer *N*-(2-naphthylmethylene)aniline *N*-oxide (**3h**) is sufficiently reactive (entry 13). It is pleasing that the nitrone **3i** derived from an aliphatic aldehyde also shows excellent diastereoselectivity as well as enantioselectivity for the *endo*-**4i** (entry 14). Thus, *the DBFOX/Ph·$Ni(ClO_4)_2$·$3H_2O$-catalyzed asymmetric nitrone cycloaddition in the presence of MS 4A has the most promising features with respect to the catalytic cycle, diastereoselectivity, and enantioselectivity among the catalyzed reactions yet reported*.

Absolute configurations of isoxazolidines *endo*-**4b**[4d] and *endo*-**4c**[5] were determined to be a 3*S*,4*R*,5*S* structure by comparison of the optical rotations as well as retention times in a chiral HPLC analysis with those of the authentic samples. Other 3,4-*trans*-isoxazolidines **4a** and **4d**−**i** were assigned by similarity of the proposed transition structures. Selection of the *Si* face at the C_β position of alkene **2a** in nitrone cycloadditions is the same as that observed in the Diels−Alder reactions of cyclopentadiene with **2a** in the presence of the (*R*,*R*)-DBFOX/Ph·$Ni(ClO_4)_2$·$3H_2O$ complex,[11] and this indicates that the s-cis conformation of alkene **2a** has participated in the reaction.

The simple structure of DBFOX complex catalysts facilitates discussion of transition structures and provides insight into the role of MS 4A. On the basis of ab initio molecular orbital calculations of a model nitrone cycloaddition,[17] a variable-temperature ^{1}H NMR study[18] of the substrate complex derived from DBFOX/Ph, $Zn(ClO_4)_2$, 3-acetyl-2-oxazolidinone, and the observed high catalytic activity, the nitrone cycloaddition in the presence of MS 4A is most likely to proceed through the transition structure TS-**A** with a trigonal-bipyramid structure (Figure 1). Face shielding by one of the 4-phenyl substituents (the top 4-phenyl) becomes very effective, and the other 4-phenyl substituent (the bottom 4-phenyl) inhibits the exo approach of nitrone **3**. As a result, the reaction shows high endo and enantioselectivities in the absence of water. In the reactions catalyzed by the aqua DBFOX complex in the absence of MS 4A, a water molecule coordinates on the nickel ion so that octahedral transition structure TS-**B** becomes predominant.[19] The reaction site of the coordinated substrate in TS-**B** is more open for the approach of nitrone **3**, and both the *Si* and *Re* faces ($C\beta$) allow the attack of nitrone **3**, showing low enantioselectivity.[14] In addition, the exo approach of nitrone **3** leading to 3,4-*cis*-isoxazolidines is not difficult, and poor endo selectivity results. Even when a trace of water is present, TS-**A** may participate predominaltly in the reaction since the octahedral complex catalyst should be less reactive than the trigonal-bipyramid complex catalyst based on the trans effect by the aqua ligand.

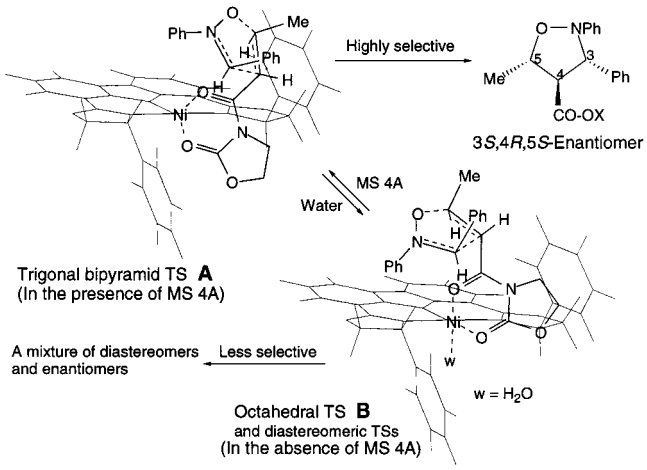

Figure 1. Proposed transition structure **A** for the endo approach of (*Z*)-nitrones leading to (3*S*,4*R*,5*S*)-isoxazolidines **4a**−**h**.

In conclusion, the aqua complex derived from the DBFOX/Ph ligand and $Ni(ClO_4)_2$·$6H_2O$ acts as excellent chiral Lewis acid catalyst in the presence of MS 4A in asymmetric 1,3-dipolar cycloadditions of nitrones to 3-(2-alkenoyl)-2-oxazolidinones. Maximum enantioselectivities observed were as high as >99% ee, and the minimum catalytic loading was 2 mol %. The presence of MS 4A is essential to attain such high selectivities. These excellent diastereoselectivities and enantioselectivities for the 3,4-*trans*-isoxazolidines with 4*S*,5*R* absolute configurations arise from the transition structure involving a trigonal-bipyramid substrate complex.

Supporting Information Available: Experimental procedures and analytical data for important compounds are contained (7 pages, print/PDF). See any current masthead page for ordering and Internet access instructions.

JA982254E

(17) Transition structures were optimized by ab initio calculations for the uncatalyzed and BH_3-catalyzed reactions of CH_2═N(O)H with CH_2═CHCHO. Bond formation of nitrone oxygen/acceptor β-carbon precedes that of nitrone carbon/acceptor α-carbon. Remarkable pyramidalization can be seen at the β-carbon of acceptor in the transition structure of the catalyzed reaction: Kanemasa, S.; Tanaka, J.; Oderaotoshi, Y. Unpublished results.

(18) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *Tetrahedron Lett.* **1998**, *39*, 7521−7524.

(19) In the variable-temperature ^{1}H NMR study cited in ref 18, an octahedral structure has been assigned to the substrate complex derived from DBFOX/Ph, $Zn(ClO_4)_2$, and 3-acetyl-2-oxazolidinone. Isomerization between two octahedral complexes should occur via the intermediacy of a trigonal-bipyramid complex.