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Enantioselective conjugate additions of aldoximes to 3-crotonoyl-2-oxazolidinone and 1-crotonoyl-3-phenyl-2-imidazolidinone catalyzed by the aqua complex between *R,R*-DBFOX/Ph and zinc(II) perchlorate

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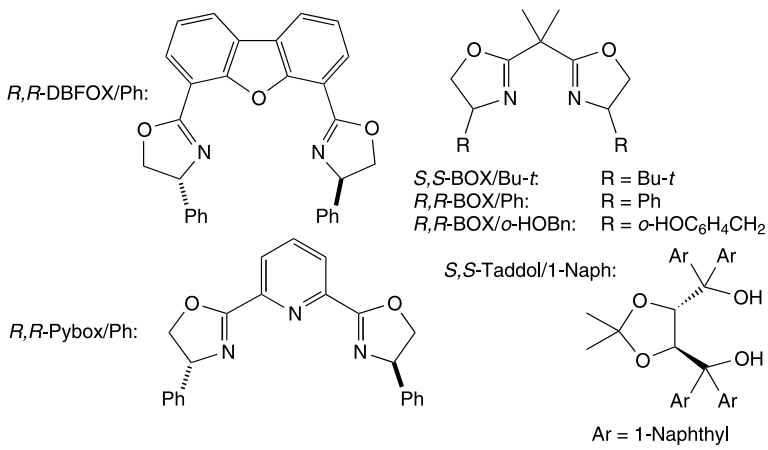
Abstract—Conjugate addition reactions of aldoximes to 3-crotonoyl-2-oxazolidinone and to 1-crotonoyl-3-phenyl-2-imidazolidinone are accelerated in the presence of a catalytic amount of Lewis acids. Among the chiral metal complexes with DBFOX/Ph, BOX/Bu-*t*, BOX/Ph, BOX/*o*-OHBn, Pybox, or TADDOL ligands, the most effective thus far is the aqua complex derived from *R,R*-DBFOX/Ph and zinc(II) perchlorate. The reaction of 2-furancarbaldehyde oxime in dichloromethane in the presence of the *R,R*-DBFOX/Ph aqua complex derived from zinc(II) perchlorate hexahydrate (10 mol%) gave a moderate enantioselectivity of 64% ee at 0°C. Reactions using other metal complexes are also discussed. © 2002 Elsevier Science Ltd. All rights reserved.

Recently, we have presented a new nitrone forming reaction by *N*-alkylation through the conjugate addition of aldoximes to α,β-unsaturated carbonyl compounds in the presence of Lewis acid catalysts.[1] The acceptors have to be unsubstituted at the β-position; use of a mixed catalyst of $ZnI_2/BF_3{\cdot}OEt_3$ (50 mol%/50 mol%) is especially effective. This conjugate addition reaction of oximes belongs to the category of 'catalytic enantioselective reactions using highly coordinating reagents', in which nucleophiles tend to bind strongly to the catalyst to cause serious deactivation of the catalytic activity.[2,3] The oxime function is well known to be an essential structural unit for strong binding of the ligands, as can be seen in the example of dimethylglyoxime. Therefore, Lewis acid-catalyzed enantioselective oxime conjugate addition reactions should be quite

Chiral ligands applied



Keywords: nitrones; aldoximes; conjugate additions; Lewis acid catalysts; *R,R*-DBFOX/Ph ligand; zinc(II) perchlorate; aqua complex; enantioselective reactions.

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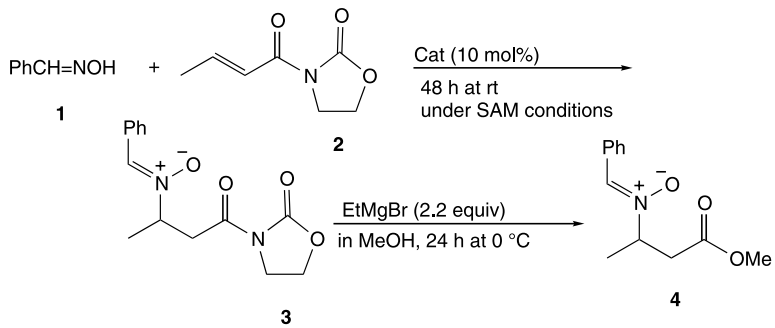
challenging. Recently, we have developed new chiral Lewis acid catalysts, which can be derived by complexation of the 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) ligand [DBFOX/Ph] with a variety of metal salts.[4] The DBFOX/Ph aqua complexes of metal salts exhibit a high tolerance to strongly coordinating nucleophiles. The questions that should be answered in the present work are: (1) can β-substituted acceptors be utilized effectively in the Lewis acid-catalyzed oxime conjugate additions? (2) Is the rate enhancement large enough in the presence of a catalytic amount of Lewis acids? (3) What is the most effective chiral catalyst in this particular case and (4) is it possible to open effective enantioselective reactions?

In the absence of Lewis acid catalysts, the reaction of (*E*)-benzaldoxime (**1**) with 3-crotonoyl-2-oxazolidinone (**2**) is too slow, and no formation of nitrone **3** could been observed even after a few days when the reaction was performed at room temperature. However, when the same reaction was carried out in the presence of titanium dichloride diisopropoxide at room temperature in dichloromethane, the corresponding nitrone **3** was produced in 67% yield after 48 h (Scheme 1). The amount of $TiCl_2(OPr\text{-}i)_2$ could be reduced to 10 mol%.

In addition, a variety of chiral Lewis acid catalysts derived from *R*,*R*-DBFOX/Ph ligand worked similarly as active catalysts. Thus, the reaction rate of the oxime conjugate addition between **1** and **2** was accelerated effectively in the presence of a catalytic amount of *R*,*R*-DBFOX/Ph complex (10 mol%). Among the catalysts examined,[5] the aqua complex derived from *R*,*R*-DBFOX/Ph and $Zn(ClO_4)_2{\cdot}6H_2O$ was especially active. When a solution of equimolar amounts of **1** and **2** in dichloromethane was added slowly, within a period of 6 h, to the solution of this catalyst, nitrone **3** was produced in 95% yield (rt, 48 h). Such effective rate enhancement by the slow addition method (SAM) over the traditional procedure (79% of **3** after 72 h) indicates that deactivation of the catalyst can be avoided under the SAM conditions. The anhydrous zinc triflate complex catalyst *R*,*R*-DBFOX/Ph·$Zn(OTf)_2$ is less effective than the aqua zinc(II) perchlorate complex *R*,*R*-DBFOX/Ph·$Zn(ClO_4)_2{\cdot}3H_2O$; replacement of dichloromethane as reaction solvent with more polar solvents such as tetrahydrofuran and acetonitrile dramatically decreases the reaction rate. Enantioselectivities observed in the reactions shown in Scheme 1 were lower than 5% ee in all cases. In order to determine the enantioselectivities, nitrone **3** was converted into its methyl ester **4** by treatment of **3** with ethylmagnesium bromide in methanol at 0°C. Subsequently, the ee values can be determined by chiral analytical HPLC using CHIRALCELL OD-H (hexane:2-propanol = 9:1 v/v).

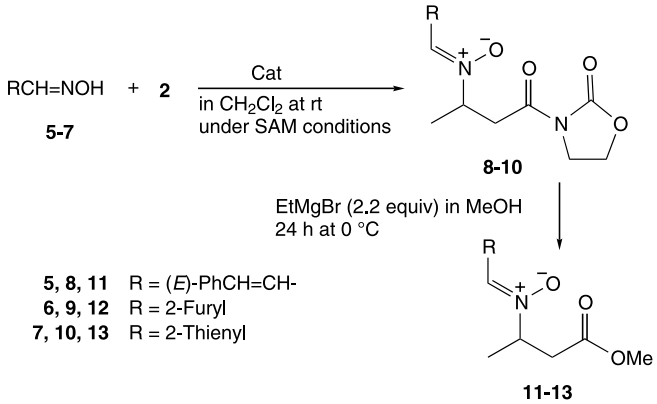
Previously, the authors have reported that the aldoximes derived from cinnamaldehyde **5**, 2-furancarbaldehyde **6**, and 2-thiophencarbaldehyde **7** are much more reactive than benzaldoxime (**1**) in oxime conjugate addition reactions under catalyzed conditions.[5] Accordingly, we have studied these more reactive aldoximes in the reactions shown in Scheme 2. When zinc(II) perchlorate hexahydrate $Zn(ClO_4)_2{\cdot}6H_2O$ (20 mol%) was utilized without the *R*,*R*-DBFOX/Ph ligand, the reactions were successfully completed within 72 h at room temperature to give the corresponding nitrones **8**–**10** in excellent yield.[6] The use of the chiral aqua complex derived from *R*,*R*-DBFOX/Ph and $Zn(ClO_4)_2{\cdot}6H_2O$ is even more effective in its catalytic activity. The nitrones were produced in high yields in shorter reaction times when 10 mol% of the catalyst was used. The enantioselectivities observed, however, were once again disappointingly poor (Scheme 2). Again the enantioselectivities were determined by transforming **8**–**10** to the methyl esters **11**–**13**, followed by the chiral HPLC measurement over CHIRALCELL OD-H (hexane:2-propanol = 2:8 v/v), or more conve-



Catalyst (10 mol%)	Solvent	Yield/%
$TiCl_2(OPr\text{-}i)_2$	CH_2Cl_2	67
R,*R*-DBFOX/Ph + $Ni(ClO_4)_2{\bullet}6H_2O$	CH_2Cl_2	71
R,*R*-DBFOX/Ph + $Zn(ClO_4)_2{\bullet}6H_2O$	CH_2Cl_2	95
R,*R*-DBFOX/Ph + $Zn(OTf)_2$	CH_2Cl_2	55
R,*R*-DBFOX/Ph + $Mg(ClO_4)_2$	CH_2Cl_2	57
R,*R*-DBFOX/Ph + $Zn(ClO_4)_2{\bullet}6H_2O$	THF	18
R,*R*-DBFOX/Ph + $Zn(ClO_4)_2{\bullet}6H_2O$	MeCN	38

SAM: Slow addition during a period of 6 h of the equimolar mixture of **1** and **2** in dichloromethane.

Scheme 1.



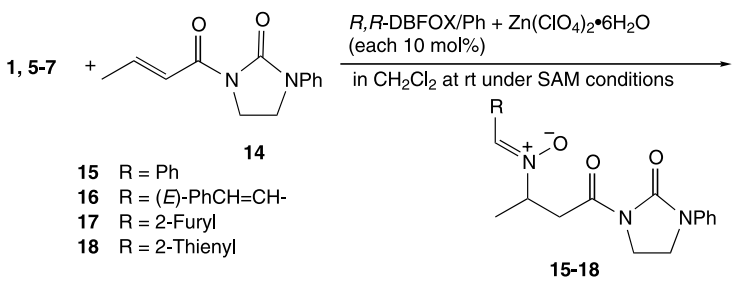
Oxime	Catalyst	mol%	Time/h	Nitrone	Yield/%	ee %
5	$Zn(ClO_4)_2•6H_2O$	20	72	**8**	82	-
6	$Zn(ClO_4)_2•6H_2O$	20	72	**9**	99	-
7	$Zn(ClO_4)_2•6H_2O$	20	72	**10**	99	-
5	*R,R*-DBFOX/Ph + $Zn(ClO_4)_2•6H_2O$	10	48	**8**	96	3
6	*R,R*-DBFOX/Ph + $Zn(ClO_4)_2•6H_2O$	10	48	**9**	86	17
7	*R,R*-DBFOX/Ph + $Zn(ClO_4)_2•6H_2O$	10	48	**10**	84	1

Scheme 2.

niently by direct selectivity measurements based on the chiral HPLC analysis over CHIRALCELL OD-H (hexane:2-propanol = 9:1 v/v) for the 2-oxazolidinone derivatives **8**–**10**.

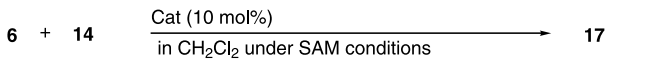
It can be easy expected that 2-imidazolidinone chelating auxiliary moiety coordinates more strongly to the catalyst than the 2-oxazolidinone unit, so that the acceptors having a 2-imidazolidinone moiety should be more reactive than the 2-oxazolidine derivatives under catalytic conditions. This anticipation is indeed correct. When the 2-oxazolidinone substrate **2** is replaced with 1-crotonoyl-3-phenyl-2-imidazolidinone (**14**) in the reaction with benzaldoxime (**1**), reactivity and enantioselectivity are both improved under SAM conditions (Scheme 3). For the reactions with such reactive oximes as **5**–**7** at room temperature, yields were satisfactory in all cases, and a medium enantioselectivity of 30% ee was recorded in the reaction of 2-furancarbaldehyde oxime (**17**). In the same reaction at 0°C, the enantioselectivity was improved to 64% ee with a chemical yield of 65%. Although a maximum enantioexcess of 67% ee could be observed in a reaction performed at the lower temperature of −40°C, the reaction was extremely slow to give **17** only in 4% yield after 72 h. Enantiomeric purity of the corresponding nitrones produced from 1-crotonoyl-3-phenyl-2-imidazolidinone (**14**) was determined by direct HPLC analysis of the imidazolidinone-substituted nitrones **15**–**18** using CHIRALCELL OD-H (hexane:2-propanol = 9:1 v/v).[7] However, the absolute configuration of the major enantiomers produced remains undetermined.

Reactions of 2-furancarbaldehyde oxime (**6**) with 1-crotonoyl-3-phenyl-2-imidazolidinone (**14**) were examined at 0°C in dichloromethane in the presence of a variety of chiral Lewis acid catalysts other than the *R,R*-DBFOX/Ph complexes (Scheme 4). Thus, a satisfactory rate enhancement was observed for the copper(II) triflate complexes of 2,2′-isopropylidenebis[(4*S*)-4-*tert*-



Oxime	Temp/°C	Time/h	Nitrone	Yield/%	ee %
1	rt	48	**15**	81	7
5	rt	48	**16**	94	nd
	0	72		59	13
6	rt	48	**17**	85	30
	0	72		65	64
	-40	72		4	67
7	0	48	**18**	94	6

Scheme 3.



Catalyst (10 mol%)	Temp/°C	Time/h	Yield/%	ee %
S,S-BOX/Bu-*t* + $Cu(OTf)_2$	rt	96	90	-15
R,R-BOX/Ph + $Cu(OTf)_2$	rt	96	58	29
R,R-BOX/o-HOBn + $Cu(OTf)_2$	rt	96	62	4
R,R-Pybox/Ph + $Zn(ClO_4)_2$•$6H_2O$	0	72	13	23
S-Binol + $TiCl_2(OPr\text{-}i)_2$	0[a]	48	39	-9
S,S-Taddol/1-Naph + $TiCl_2(OPr\text{-}i)_2$	0[a]	48	78	-36

[a] MS 4A 100 mg/0.1 mmol

Scheme 4.

butyl-2-oxazoline) *S,S*-BOX/Bu-*t*·$Cu(OTf)_2$, 2,2′-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline) *R,R*-BOX/Ph·$Cu(OTf)_2$, 2,2′-isopropylidenebis[(4*R*)-4-(2-hydroxybenzyl)-2-oxazoline) *R,R*-BOX/*o*-OHBn·$Cu(OTf)_2$ and the titanium(IV) complex prepared from (*R,R*)-(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(di-1-naphthylmethanol) and titanium dichloride diisopropoxide. However, the zinc(II) perchlorate aqua complex of 2,6-pyridinediyl-2,2′-bis[(4*R*)-4-phenyloxazoline] *R,R*-Pybox/Ph·$Zn(ClO_4)_2$·*n*H_2O and the titanium(IV) complex prepared from (*S*)-1,1′-bi-2-naphthol and titanium dichloride diisopropoxide failed to accelerate the reaction. The copper(II) complex *S,S*-BOX/Bu-*t*·$Cu(OTf)_2$ was an especially active catalyst to give nitrone **17** in 90% yield, with an enantioselectivity of only 15% ee. The titanium taddolate-catalyzed reaction provided the product in 36% ee, still is not satisfactory enantioselectivity.

In conclusion, it has been found that the conjugate addition reactions of aldoximes can be successfully accelerated by a catalytic amount (10 mol%) of Lewis acid when using acceptor substrates having β-substituents. The aqua complex derived from *R,R*-DBFOX/Ph and zinc(II) perchlorate hexahydrate is an especially active catalyst and 1-(2-alkenoyl)-3-phenyl-2-imidazolidinones are much better acceptors than 3-(2-alkenoyl)-2-oxazolidinones. With this aqua zinc(II) complex catalyst, a moderate enantioselectivity of 64% ee has been obtained in the reaction between 2-furancarbaldehyde oxime with 1-crotonoyl-3-phenyl-2-imidazolidinone in dichloromethane at 0°C. Further work to optimize the catalyzed reactions is now in progress.

Acknowledgements

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5. See Ref. 1. Some other related data have not been published (Nakama, K.; Kanemasa, S.).
6. 1-[3-(2-Furylmethyleneamino)butanoyl]-3-phenyl-2-imidazolidinone *N*-oxide (**9**): The enantiomeric excess was estimated to be 64% ee on the basis of analytic chiral HPLC over CHIRALCELL OD-H with hexane:*i*-PrOH (20:80 v/v), $[\alpha]_D^{20} = -54.0$ ($c = 10$, $CHCl_3$). Colorless solid, mp 203–204°C, ^{1}H NMR ($CDCl_3$) $\delta = 1.56$ (3H, d, $J = 6.8$ Hz), 3.12 (1H, dd, $J = 18.1$ and 2.9 Hz), 3.8–3.9 (4H, m), 4.72 (1H, dd, $J = 18.1$ and 9.7 Hz), 4.72 (1H, m), 6.53 (1H, m), 7.16 (1H, t, $J = 7.5$ Hz), 7.38 (2H, t, $J = 7.5$ Hz), 7.47 (1H, m), 7.52 (2H, d, $J = 2.9$ Hz), 7.74 (1H, d, $J = 2.9$ Hz), and 7.79 (1H, s), ^{13}C NMR ($CDCl_3$) $\delta = 19.60$, 38.73, 39.33, 41.71, 65.69, 112.18, 115.25, 118.97, 124.49, 125.49, 129.00, 138.49, 143.50, 146.79, 152.42, and 170.48. FAB Mass *m*/*z* (rel. intensity, %) 342 (17, M^+), 341 (5), 308 (7), 231 (15), 180 (7), 163 (7), 155 (26),153 (5),152 (7), 139 (10), 138 (28), 137 (56), 135 (7), 124 (7), 121 (5), 120 (10), 108 (5), 91 (7), 90 (8), and 89 (11), IR (KBr, cm^{-1}) 3417, 3313, 3193, 3136, 3066, 2981, 2904, 1735, 1666, 1596, 1558, 1485, 1458, 1400, 1369, 1292, 1253, 1215, 1176, 1161, 1130, 1103, 1083, 1033, 1010, 941, 887, 829, 756, 694, 667, 632, 594, 536, 513, 470 443, and 412. FAB HRMS (70 eV) calcd for $C_{16}H_{20}N_3O_4$: *m*/*z* 342.1376 (M^+). Found: *m*/*z* 342.1455.
7. Nitrone **15** has been prepared quantitatively by the reaction of 1-[3-(*N*-benzylhydroxylamino)butanoyl]-2-phenyl-2-imidazolidinone with a catalytic amount (10 mol%) of copper(II) triflate in dichloromethane at room temperature in the presence of air (Kanemasa, S.; Miura, A., unpublished result).