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Enantioselective Synthesis of *cis*-2-Oxazoline-4-carboxylates by Lewis Acid Catalyzed Formal [3 + 2] Cycloadditions of 5-Alkoxyoxazoles with Aldehydes

Hiroyuki Suga,* Kosei Ikai, and Toshikazu Ibata*

Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560, Japan

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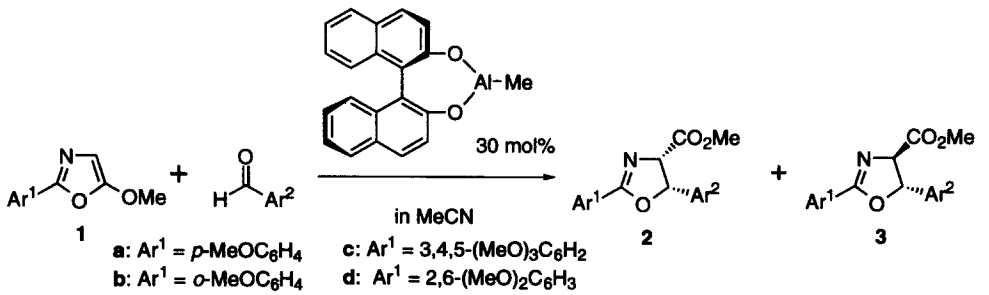
Abstract: Formal [3 + 2] cycloaddition of 2-*o*-methoxyphenyl-5-methoxyoxazole with benzaldehyde, *m*- and *p*- substituted benzaldehydes in the presence of 30 mol% of (*R*)-methylaluminum ß-binaphthoxide, which was prepared from (*R*)-2,2'-dihydroxy-1,1'-dinaphthyl and 1.1 – 1.05 equiv. of trimethylaluminum, gave *cis*-2-oxazoline-4-carboxylates in high enantioselectivity.

The importance of enantioselective synthesis of 2-oxazoline-4-carboxylates in modern synthetic methodology is apparent from the numerous synthetic applications using 2-oxazoline-4-carboxylates as the building blocks of ß-hydroxy amino acids and 2-amino-1,3-diols.[1-5] 5-Substituted 2-oxazoline-4-carboxylates have *cis*- and *trans*-isomers at the relative configuration of 4- and 5-positions, and the transformation of *cis*- and *trans*-isomers gives *threo*- and *erythro* ß-hydroxy amino acids or 2-amino-1,3-diols, respectively. In view of the synthetic utility of 2-oxazoline-4-carboxylates, methodology for the stereo- and enantioselective synthesis of these compounds is needed. For the enantioselective synthesis of *trans*-2-oxazoline-4-carboxylates, ferrocenylphosphine-gold(I) complexes were found to be the most effective catalyst in the reaction of isocyanoacetate with aldehydes.[3] However, enantioselective synthesis of *cis*-2-oxazoline-4-carboxylates has not been reported yet.[5] Recently, we reported that regio- and stereoselective formal [3 + 2] cycloadditions of 2-aryl-5-methoxyoxazoles with aldehydes catalyzed by a stoichiometric amount of racemic methylaluminum ß-binaphthoxide gave *cis*-2-oxazoline-4-carboxylates.[6] We also proved that the diastereoselective formal cycloaddition of 5-methoxy-oxazoles with chiral β-alkoxyaldehydes is extremely useful for the synthesis of optically pure 2-amino-1,3,4-triols.[7] In this paper, we report the first example of highly enantioselective synthesis of *cis*-2-oxazoline-4-carboxylates in the formal [3 + 2] cycloadditions of 2-*o*-methoxypheny-5-methoxyoxazole with aldehydes catalyzed by 30 mol% of chiral methylaluminum ß-binaphthoxide.



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Reactions of four oxazoles **1a** – **1d** with benzaldehyde were carried out in the presence of 30 mol% of the chiral catalyst under the conditions listed in Table 1. We found that all the reactions proceeded by catalytic amounts of (*R*)-methylaluminum ß-binaphthoxide using 10 equiv. of benzaldehyde to give 2-oxazoline-4-carboxylates in high yield. The enantioselectivity was determined to be high (74 - 88 % ee) by chiral HPLC (DAICEL Chiralcel AS, i-PrOH / hexane = 1 : 9). In the presence of 30 mol% of the catalyst under optimum conditions, 2-*o*-methoxyphenyloxazole **1b** showed the highest enantioselectivity (84 – 87% ee) of *cis*-adduct (entries 4 and 5).[8] It is interesting to note, for the preparation of the catalyst, slight excess (1.1 – 1.05 equiv.) of trimethylaluminum was needed to obtain reproducibility in terms of high enantioselectivity and yield (entries 4 and 5) in the reactions of **1b**. However, in the reactions of oxazole **1a** and **1c**, almost the same or less enantioselectivity was obtained by using slight excess of trimethylaluminum to (*R*)-2,2'-dihydroxy-1,1'-dinaphthyl ((*R*)-BINOL) than by mixing $AlMe_3$ and (*R*)-BINOL in 1 : 1 ratio. In the case of oxazole **1a**, the enantioselectivity in the catalytic reaction decreased compared with that under the stoichiometric conditions (entries 1, 2 and 3). *O*-Methoxy substitutions on the 2-aryl group of oxazoles accelerated the reaction rate in comparison with oxazoles **1a** and **1c** but slightly lowered the *cis*-selectivity (entries 4, 5 and 7). The reaction of oxazole **1c** showed a lower yield than other oxazoles, probably due to the lower reactivity (entry 6).

Table 1. Reactions of Oxazoles **1a** – **1d** with Benzaldehyde in the Presence of 30 mol% of (*R*)-Methylaluminum β-Binaphthoxide[a)]

Entry	Oxazole	Conditions	Yield,%	*cis*:*trans*	ee, % (*cis*)[b)]	Config. (*cis*)[9]
1	**1a**	rt, 46 h[c)]	82	93:7	74	(4*S*,5*S*)
2	**1a**	– 10 °C, 89 h[d)]	89	96:4	75	(4*S*,5*S*)
3	**1a**	– 10 °C, 89 h[e)]	81	92:8	88	(4*S*,5*S*)
4	**1b**	5 °C, 27 h[f)]	92	85:15	84	(4*S*,5*S*)
5	**1b**	5 °C, 49 h[g)]	82	83:17	87	(4*S*,5*S*)
6	**1c**	rt, 42 h	64	94:6	84	(4*S*,5*S*)
7	**1d**	5 °C, 50 h	83	59:41	80	(4*S*,5*S*)

a) The reaction was carried out with 10 equiv. of benzaldehyde in the presence of 30 mol% of methylaluminum β-binaphthoxide which was prepared from Me_3Al and (*R*)-BINOL unless otherwise noted.
b) Determined by HPLC analysis using CHIRAL PAK AS (hexane / i-PrOH = 9 : 1, flow 0.5 ml/min). The enantiomeric excesses of *trans*-2-oxazoline-4-carboxylates were 8% to 32%.
c) The catalyst was prepared from Me_3Al and (*R*)-BINOL in 1 : 1 ratio.
d) The reaction was carried out in the presence of 50 mol% of methylaluminum β-binaphthoxide.
e) The reaction was carried out with 3 equiv. of benzaldehyde in the presence of 2 equiv. of methylaluminum β-binaphthoxide.
f) The catalyst was prepared from Me_3Al and (*R*)-BINOL in 1.05 : 1 ratio.
g) The catalyst was prepared from Me_3Al and (*R*)-BINOL in 1.1 : 1 ratio.

Oxazoles **1a**, **1b**, and **1c** also underwent the formal [3 + 2] cycloaddition with several kinds of *p*- and *m*-substituted benzaldehydes to give the corresponding 2-oxazoline-4-carboxylates in high enantioselectivity (Table 2). The reaction of oxazole **1b** with substituted benzaldehydes showed higher enantioselectivities (76%ee – 90% ee) of *cis*-adducts than the reaction of other oxazoles independent of the substituents. In the

reactions with *p*-nitro- and *p*-cyanobenzaldehydes, oxazole **1c** showed higher *cis*-selectivity with similar degree of enantioselectivity to those in the reaction of **1b** (Table 2, entries 2, 3, 4 and 5).

Table 2. Reactions of Oxazole **1a** -**1c** with Aromatic Aldehydes in the Presence of 30 mol% of (*R*)-Methylaluminum β-Binaphthoxide[a)]

Entry	Oxazole	Aldehyde	Conditions	Yield, %	*cis:trans*	ee, % (*cis*)[b)]
1	**1a**	*p*-$NO_2C_6H_4CHO$	–10 °C, 21 h[c)]	91	87:13	64[d)]
2	**1b**	*p*-$NO_2C_6H_4CHO$	–10 °C, 21 h[e)]	83	43:57	76[d)]
3	**1c**	*p*-$NO_2C_6H_4CHO$	5 °C, 70 h[c)]	74	88:12	75
4	**1b**	*p*-CNC_6H_4CHO	5 °C, 24 h[e)]	52	71:29	76
5	**1c**	*p*-CNC_6H_4CHO	5 °C, 75 h[c)]	60	90:10	75
6	**1b**	*p*-ClC_6H_4CHO	5 °C, 24 h[e)]	89	83:17	87
7	**1b**	*p*-MeC_6H_4CHO	5 °C, 43 h[e)]	72	88:12	84
8	**1b**	*p*-$MeOC_6H_4CHO$	rt, 70 h[e)]	57	54:46	89
9	**1a**	*m*-$NO_2C_6H_4CHO$	5 °C, 15 h[e)]	89	90:10	82
10	**1b**	*m*-$NO_2C_6H_4CHO$	5 °C, 15 h[e)]	85	73:27	84
11	**1a**	*m*-ClC_6H_4CHO	5 °C, 42 h[c)]	75	91:9	78
12	**1b**	*m*-ClC_6H_4CHO	5 °C, 42 h[e)]	82	83:17	84
13	**1a**	*m*-MeC_6H_4CHO	5 ° C, 117 h[e)]	61	93:7	81
14	**1b**	*m*-MeC_6H_4CHO	5 ° C, 117 h[e)]	51	88 :12	88
15	**1a**	*m*-$MeOC_6H_4CHO$	5 °C, 45 h[c)]	66	97:3	78
16	**1b**	*m*-$MeOC_6H_4CHO$	5 °C, 45 h[c)]	70	87:13	90

a) The reaction was carried out with 10 equiv. of benzaldehyde in the presence of 30 mol% of methylaluminum β-binaphthoxide which was prepared from Me_3Al and (*R*)-BINOL unless otherwise noted.
b) Determined by HPLC analysis using CHIRAL PAK AS (hexane / i-PrOH = 9 : 1, flow 0.5 ml/min). The enantiomeric excesses of *trans*-2-oxazoline-4-carboxylates were 5% to 46%.
c) The catalyst was prepared from Me_3Al and (*R*)-BINOL in 1 : 1 ratio.
d) Determined by ^1H NMR using (*R*)-BINOL as shift reagent.
e) The catalyst was prepared from Me_3Al and (*R*)-BINOL in 1.05 : 1 ratio.

3-Thiophenecarboxyaldehyde also underwent cycloaddition with oxazole **1b** in moderate selectivity (*cis* : *trans* = 84 : 16, *cis*: 63% ee) in low yield (19%). Unfortunately, the reaction of cinnamaldehyde and 2-thiophenecarboxyaldehyde resulted in low yield (11% and 28%), *trans*-selectivity (*trans* : *cis* = 70 : 30 and 90 : 10) and low enantioselectivity (*trans*: 38% ee and 36 % ee).

The general procedure is as follows: To a solution of (*R*)-BINOL (85.9 mg, 0.30 mmol) in MeCN (6.0 mL) was added 1.05 M hexane solution of Me_3Al (0.30 mL, 0.315 mmol). The resulting mixture was stirred at rt for 1 h. After the mixture was cooled to –20 °C, a solution of oxazole **1b** (0.205 g, 1.0 mmol) and benzaldehyde (1.06 g, 1.02 mL, 10.0 mmol) in MeCN (9.0 mL) was added dropwise to the solution. The mixture, after stirring at 5 °C for 27 h, was quenched with saturated solution of $NaHCO_3$. The product was extracted with CH_2Cl_2 (30 mL x 3), the separated organic layer was dried over anhydrous $MgSO_4$, and the

solvent was removed from the organic solution under reduced pressure. 2-Oxazolines **2b** and **3b** were isolated by medium-pressure liquid chromatography on silica gel with hexane-ethyl acetate as an eluent.

In conclusion, the above-described methodology involving the chiral methylaluminum ß-binaphthoxide-catalyzed formal [3 + 2] cycloaddition of 5-alkoxyoxazoles with aldehydes has the advantage of high enantio- and *cis*-selectivity over previous methods for the synthesis of 2-oxazoline-4-carboxylates.

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