Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides Generated in situ by Direct Oxidation of Aldoximes

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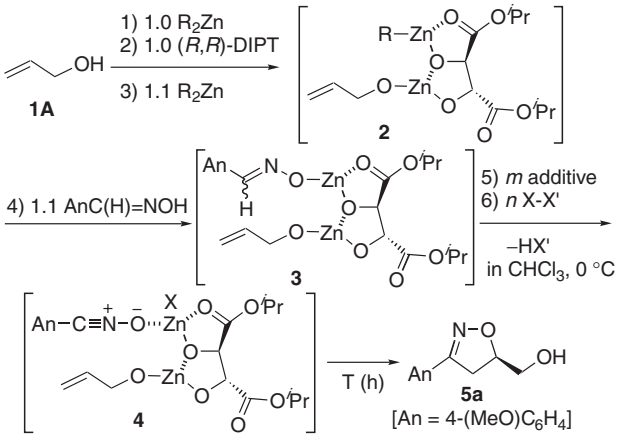
The asymmetric 1,3-dipolar cycloaddition of nitrile oxides, generated in situ from aldoximes by direct oxidation with *tert*-butyl hypochlorite, to 2-propen-1-ol was achieved by utilizing diisopropyl (*R*, *R*)-tartrate as a chiral auxiliary to afford the corresponding (*R*)-2-isoxazolines with high enantioselectivity up to 96% ee.

Asymmetric 1,3-dipolar cycloaddition nowadays attracts a great deal of attention in synthetic organic chemistry, because it can provide optically active five-membered ring compounds. Above all, the asymmetric 1,3-dipolar cycloaddition of nitrone to olefins has been recently extensively studied and several efficient methods were reported using chiral Lewis acids.[1] To the contrary, the enantioselective 1,3-dipolar cycloaddition of nitrile oxide had not yet to meet with success although diastereoselective reactions to the olefins bearing a chiral auxiliary have been reported.[1a,2] One reason is that nitrile oxide is generally unstable and is necessary to be generated in situ from hydroximoyl halide by dehydrohalogenation or from primary nitro compound by dehydration.[3]

We have developed the first and probably only, so far we know, enantioselective 1,3-dipolar cycloaddition of nitrile oxides to allylic alcohols utilizing diisopropyl tartrate (DIPT) as a chiral auxiliary to give the corresponding 2-isoxazolines with excellent enantioselectivity,[4] and the reaction was successfully applied to the synthesis of Lythraceae alkaloid, lasubine II.[4d] In our method, nitrile oxide was generated in situ from hydroximoyl chloride by treating with alkylzinc reagent as a base. It is well-known that hydroximoyl chloride is rather labile compared with the corresponding aldoxime, but nitrile oxide can be also generated in situ from the aldoxime by treatment with sodium hypochlorite. If the enantioselective 1,3-dipolar cycloaddition of nitrile oxide could be realized using aldoxime as a source of nitrile oxide, the reaction would become quite convenient and efficient. Herein we would like to describe the enantioselective 1,3-dipolar cycloaddition of nitrile oxides generated in situ by direct oxidation of aldoximes.

When 2-propen-1-ol (**1A**) is successively treated with dialkylzinc, (*R*, *R*)-DIPT, a second dialkylzinc, and aldoxime, the zinc-bridging intermediate **3** is presumably formed. By the addition of halogenating agent (X–X′) as an oxidant to the putative intermediate **3**, oxidation of the aldoxime residue might proceed to generate HX′ and nitrile oxide, which would coordinated to zinc metal as depicted in **4**, and followed by asymmetric 1,3-dipolar cycloaddition to give the corresponding 2-isoxazoline **5** in optically active form. According to this hypothesis, the asymmetric 1,3-dipolar cycloaddition was investigated in detail.



First, several oxidants were examined as shown in Table 1; i.e., to 2-propen-1-ol (**1A**) was successively added dimethylzinc (1.0 molar amount), (*R*, *R*)-DIPT (1.0 molar amount), a second dimethylzinc (1.1 molar amounts), *p*-methoxybenzaldehyde oxime (1.1 molar amounts), and finally an oxidant (*n* molar amounts) in $CHCl_3$ at 0 °C. Although the corresponding 2-isoxazoline **5a** was obtained by the use of *N*-chlorosuccinimide (NCS) as an oxidant,[5] the enantioselectivity was low (Entry 1). The use of *N*-bromosuccinimide (NBS) instead of NCS gave the isoxazoline **5a** with lower enantioselectivity (Entry 2). The oxidation by *N*-iodosuccinimide (NIS) and ICl gave only a trace

Table 1. Asymmetric 1,3-dipolar cycloaddition of a nitrile oxide generated in situ by the direct oxidation of an aldoxime[a]

Entry	R	X–X′	*n*	Additive	*m*	T/h	Yield/%	ee/%[b]
1	Me	NCS	1.1	—	—	13	71	26
2	Me	NBS	1.1	—	—	13	38	19
3	Me	NIS	1.1	—	—	13	trace	—
4	Me	I–Cl	1.1	—	—	15	trace	—
5	Me	Cl–O^{t}Bu	1.1	—	—	14	35	73
6	Et		1.1	—	—	14	19	53
7	^{i}Pr		1.1	—	—	15	39	88
8	^{i}Pr		2.0	—	—	17	73	92
9	^{i}Pr		3.0	—	—	18	81	85
10[c]	^{i}Pr		2.0	^{t}BuOH	0.01	18	64	90
11[c]	^{i}Pr		2.0	^{t}BuOH	0.1	12	69	82
12[c]	^{i}Pr		2.0	1,4-dioxane	1.5	11	66	90
13[d]	^{i}Pr		2.0	1,4-dioxane	1.5	16	76	93

[a]Reaction was carried out on a 0.5 mmol scale in 9 ml $CHCl_3$. [b]Enantioselectivities were determined by HPLC analysis (Daicel Chiralcel OD-H). [c]Reaction was carried out on a 0.5 mmol scale in 12 ml $CHCl_3$. [d]Reaction was carried out on a 1.4 mmol scale in 12 ml $CHCl_3$.

amount of cycloadduct (Entries 3, 4). The enantioselectivity was enhanced by utilizing *tert*-butyl hypochlorite[6] though chemical yield was poor (Entry 5).[7] Other oxidants, such as $BrCCl_3$, 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one, and benzyltrimethylammonium tetrachloroiodate[8] produced no isoxazoline. In order to improve the chemical and optical yields, the alkyl group of dialkylzinc and the molar amounts of *tert*-butyl hypochlorite were varied. When diisopropylzinc was used instead of dimethylzinc or diethylzinc, enantioselectivity was considerably improved (Entries 5–7)[9] and the use of 2.0 molar amounts of oxidant realized over 90% ee (Entries 7–9). Unfortunately, the enantioselectivity was fluctuated to a great extent depending on the used *tert*-butyl hypochlorite. *tert*-Butyl alcohol, produced with the progress of the reaction, was suspected to influence on the reproducibility. Thus, the reaction was carried out in the presence of a small amount of *tert*-butyl alcohol to afford **5a** with reproducible good to high enantioselectivities (Entries 10, 11). As *tert*-butyl alcohol seemed to dissociate the unfavorable aggregation of the intermediary zinc complex **4** for the ideal reaction course, 1,4-dioxane was added as an additive[4b] resulting in the similar reproducibility (Entry 12). Finally, by carrying out the reaction at higher concentration (Entry 13), both the chemical yield and enantioselectivity were improved to 76% and 93% ee, respectively.[10]

Next, the asymmetric cycloaddition of several nitrile oxides to allylic alcohols **1** was performed. After optimizing the molar quantities of diisopropylzinc, aldoxime, and *tert*-butyl hypochlorite, the corresponding 2-isoxazolines **5** could be obtained in excellent optical yields (Table 2).[11]

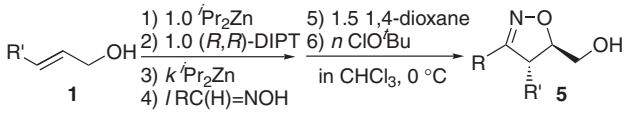
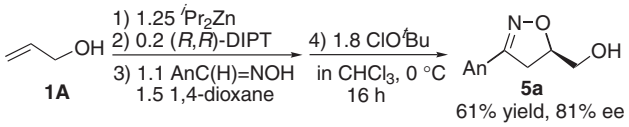


Table 2. Asymmetric 1,3-dipolar cycloaddition of nitrile oxides generated in situ by the direct oxidation of aldoximes with *tert*-butyl hypochlorite[a]

Entry	R′	**1**	R	*k*	*l*	*n*	**5**	Yield/%	ee/%
1	H	**A**	4-(MeO)C_6H_4	1.1	1.1	2.0	**a**	76	93[b]
2			Ph	1.1	1.1	2.0	**b**	77	92[c]
3			4-ClC_6H_4	1.1	1.1	2.0	**c**	75	92[b]
4			Heptyl	2.05	3.0	4.0	**d**	63	90[b]
5			^{t}Bu	1.1	1.1	2.0	**e**	71	96[c]
6[d]	CO_2Et	**B**	4-(MeO)C_6H_4	1.1	1.1	2.0	**f**	30	89[b]

[a]Reaction was carried out on a 1.4-1.5 mmol scale in 12 ml $CHCl_3$ for 15–19 h. [b]Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H). [c]Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OB-H). [d]Reaction was carried out at 25 °C.

The present asymmetric 1,3-dipolar cycloaddition was found to proceed well even with the catalytic amount of (*R*, *R*)-DIPT, though the reaction conditions were not yet optimized, to afford the corresponding 2-isoxazoline with good enantioselectivity.



As described above, efficient enantioselective 1,3-dipolar cycloaddition of nitrile oxide generated in situ from aldoxime by the direct oxidation was realized. The present procedure has the great advantage not to involve the preparation of rather unstable hydroximoyl chloride. Because of easy availability of (*R*, *R*)- and (*S*, *S*)-DIPT, this method provides a useful way to prepare both enantiomers of 2-isoxazolines which are the versatile intermediates for optically active β-hydroxy ketones or γ-amino alcohols.

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9 If the intermediate **3** was produced completely by the reaction of alkylzinc moiety in **2** with aldoxime, the kind of alkyl group in dialkylzinc would not influence the chemical yield and enantioselectivity. The fact that those were altered depending on the used dialkylzinc might indicate the incompletion of the reaction of methyl- and ethylzinc moiety in **2** with aldoxime.
10 Recently we found a concentration effect for the 1,3-dipolar cycloaddition of a nitrone to give the corresponding isoxazolidines with higher enantioselectivity in higher chemical yield: D. Xia, Y. Ukaji, S. Fujinami, and K. Inomata, *Chem. Lett.*, **2002**, 302.
11 A representative procedure is as follows: To a $CHCl_3$ (3 ml) solution of 2-propen-1-ol (**1A**) (84 mg, 1.4 mmol) was added diisopropylzinc (1.4 mmol, 1.4 ml of 1.0 mol l^{-1} solution in hexane) at 0 °C under an argon atmosphere, and the mixture was stirred for 10 min. Then a $CHCl_3$ (3 ml) solution of (*R*, *R*)-DIPT (339 mg, 1.4 mmol) was added and the mixture was stirred for 1 h. Diisopropylzinc (1.6 mmol), a $CHCl_3$ (3 ml) solution of *p*-methoxybenzaldehyde oxime (240 mg, 1.6 mmol), a $CHCl_3$ (3 ml) solution of 1,4-dioxane (192 mg, 2.2 mmol), and a $CHCl_3$ (3 ml) solution of *tert*-butyl hypochlorite (314 mg, 2.9 mmol) were successively added every 10 min and the resulting solution was stirred for 16 h at 0 °C. The reaction was quenched by addition of saturated aq NH_4Cl and $NaHSO_3$. Purification by column chromatography on silica gel afforded 2-isoxazoline **5a** (227 mg, 76%) in 93% ee.