Regio- and diastereo-selective formation of isoxazoline derivatives by Lewis acid mediated 1,3-dipolar cycloaddition reactions of nitrile oxide

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In the presence of magnesium perchlorate, 1,3-dipolar cycloaddition reactions of nitrile oxides to crotonamide bearing 4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one as the chiral auxiliary proceeded with a regio- and diastereo-selective manner to afford the corresponding chiral 2-isoxazoline. The mechanisms underlying the diastereoface selection in the cycloaddition reaction were investigated using the B3LYP/6-31G* level of theory.

Keywords: asymmetric synthesis, chiral auxiliaries, regioselectivity, diastereoselectivity, nitrile oxide

Nitrile oxides are very useful chemical species in organic synthesis, yielding five-membered heterocyclic compounds in 1,3-dipolar cycloaddition reactions with various dipolarophiles.[1] Nitrile oxides not only react rapidly even at temperatures as low as –78°C to form the corresponding isoxazolines, but are also so reactive that they irreversibly form dimers by reacting with themselves. Therefore stereocontrol in cycloaddition reactions of nitrile oxides is a problem that needs much study.[2] We recently reported that the addition of magnesium salts and ytterbium salts causes a significant increase in diastereoselectivity in reactions of nitrile oxides with electron-deficient dipolarophiles bearing an oxazolidinone chiral auxiliary.[3,4] The dipolarophile used in these studies is a mono-substituted alkene, so the reaction proceeds regioselectively. However, when a reaction with a 1,2-disubstituted alkene is performed with the aim of synthesis of multi-substituted heterocyclic, a mixture of regioisomers is usually obtained. Therefore, we now report on the Lewis acid mediated regio- and diastereo-selective cycloaddition of nitrile oxides with a chiral 1,2-disubstituted alkene.[5-7]

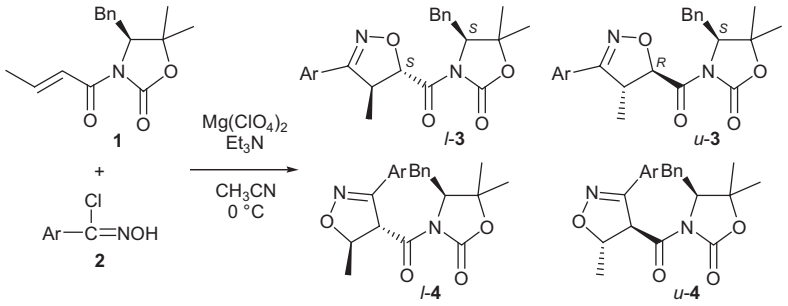
Scheme 1 and Table 1 summarise the results of cycloaddition reactions between benzonitrile oxides and dipolarophile **1**. Although the reaction gave a mixture of four stereoisomers of the corresponding isoxazolines in the absence of a catalyst, it was confirmed that addition of an equimolar amount of magnesium perchlorate remarkably improved the both of regioselectivity and diastereoselectivity in the cycloaddition reactions. The cycloaddition reaction with benzonitrile oxide bearing an electron-donating group proceeded with higher selectivities than the reaction with benzonitrile oxide with an electron-withdrawing group. It is interesting to note that despite the addition of a Lewis acid that has hitherto been said to reduce the reactivity of nitrile oxides, the yield of the objective isoxazoline was also found to be markedly better than in the case where it is not added.

Transition state (TS) search is the key to understanding reaction mechanisms in detail, for example, why good selectivity for a target was achieved. Density functional theory (DFT) calculations at the B3LYP/6-31G* level of theory were used to optimise the geometry of TSs in the cycloaddition reaction of dipolarophile **1** and benzonitrile oxide, in which the regioselectivity was found to be 92 : 8 and the diastereoselectivities were 86 : 14 (*l*-**3**/*u*-**3**)[8] and 79 : 21 (**4**) in the presence of $MgBr_2$, using the Gaussian 03 program.[9] According to the DFT calculations, the formation of cycloadducts *l*-**3a**, *u*-**3a**, and *l*-**4a** proceed *via* transition states *l*-**3a(TS)**, *u*-**3a(TS)**, and *l*-**4a(TS)**, respectively (Fig. 1). No stable structure for the TS leading to *u*-**4a** was obtained because of the critical betwee steric repulsion n phenyl group in nitrile oxide and benzyl group in dipolarophile. As shown in Fig. 1, the *l*-**3a(TS)** was calculated to be more stable by 3.67 kcal/mol than *u*-**3a(TS)** and by 3.28 kcal/mol than *l*-**4a(TS)**. Therefore formation of *l*-**3a** was the most favourable by the cycloaddition reaction of benzonitrile oxide and **1a** in the presence of $MgBr_2$.

To summarise, the addition of magnesium perchlorate can bring about significant improvements in regio- and diastereo-selectivity in the nitrile oxide cycloaddition reactions with 4-benzyl-3-crotonoyl-5,5-dimethyl-1,3-oxazolidin-2-one, to afford chiral 5-acylisoxazolines with high chemical yield.

Experimental

All of commercially available reagents were used without further purification. Reaction solvents were dried by standard method before use. ^{1}H NMR spectra were recorded at 270 MHz and ^{13}C NMR spectra were recorded at 67.8 MHz with a JEOL EX-270 spectrometer in $CDCl_3$ solutions. Optical rotations were measured with a JASCO DIP-140 digital polarimeter. The progress of reactions was monitored by TLC (silica gel 60F-254, Merck). Chromatographic purification was performed with Wakogel C-200 (100–200 mesh, Wako Pure Chemical Industries) and/or silica gel 60 (230–400 mesh, Merck).



Scheme 1

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Table 1 Regio- and diastereo-selective 1,3-dipolar cycloaddition reactions between *p*-substituted benzonitrile oxide and **1**

Ar	$Mg(ClO_4)_2$	Regioselectivity[a]	Diastereoselectivity[a,b]			
	equiv.	**3**/**4**		*l*-**3**/*u*-**3**		**4**
Ph	0	66:34	**3a**	41:59 (61)	**4a**	58:42 (23)
Ph	1	98:2	**3a**	95:5 (85)	**4a**	-:- (-)
p-MeO-C_6H_4	0	63:37	**3b**	40:60 (52)	**4b**	56:44 (36)
p-MeO-C_6H_4	1	96:4	**3b**	94:6 (80)	**4b**	94:6 (3)
p-Cl-C_6H_4	0	68:32	**3c**	43:57 (51)	**4c**	58:42 (26)
p-Cl-C_6H_4	1	94:6	**3c**	88:12 (83)	**4c**	60:40 (4)
p-F-C_6H_4	0	67:33	**3d**	40:60 (36)	**4d**	58:42 (18)
p-F-C_6H_4	1	94:6	**3d**	91:9 (67)	**4d**	65:35 (4)
p-O_2N-C_6H_4	0	80:20	**3e**	43:57 (30)	**4e**	68:32 (7)
p-O_2N-C_6H_4	1	86:14	**3e**	69:31 (64)	**4e**	50:50 (12)

[a]Determined by ^{1}H NMR. [b]Isolated yield is in the parenthesis.

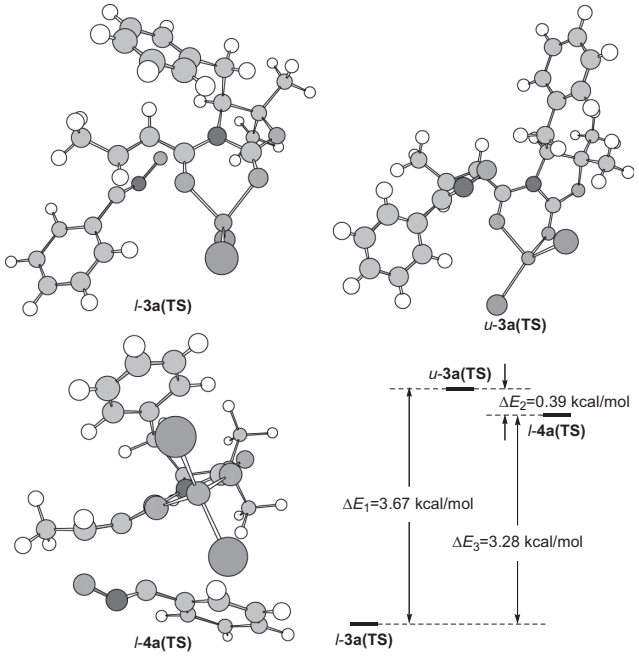

Fig. 1 Structure of transition states in the cycloaddition reaction of dipolarophile 1 and benzonitrile oxide

General procedure for magnesium perchlorate mediated cycloaddition reactions of nitrile oxides

To magnesium perchlorate (55.8 mg, 0.250 mmol) was added a solution of dipolarophile **1** (68.3 mg, 0.250 mmol) and arylhydroximoyl chloride (0.275 mmol) in dry CH_3CN (0.125 ml) under N_2, and stirred for 20 min at room temperature. After cooling to 0°C, triethylamine (42.0 µl, 0.300 mmol) was added. The mixture was stirred for 12 h at 0°C, quenched with brine, and extracted with ethyl acetate (5 ml × 4). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The residue was chromatographed on silica gel with hexane-ethyl acetate as an eluent to afford the cycloadduct **3** and **4** as a mixture of diastereoisomers, respectively. The major isomer *l*-**3** was isolated by recrystallisation.

l-**3a**: Colourless needles (from CH_2Cl_2–hexane); m.p. 180.5–181.5°C; $[\alpha]_D^{28}$ = 94.0° (*c* 1.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 1.37 (3H, s, one of Me-5), 1.43 (3H, s, the other of Me-5), 1.50 (3H, d, *J* = 7.3 Hz, Me-4'), 2.88 (1H, dd, *J* = 14.2, 9.9 Hz, one of CH_2Ph), 3.27 (1H, dd, *J* = 14.2, 3.3 Hz, other of CH_2Ph), 3.81 (1H, dq, *J* = 7.3, 2.6 Hz, H-4'), 4.46 (1H, dd, *J* = 9.9, 3.3 Hz, H-4), 5.77 (1H, d, *J* = 2.6 Hz, H-5'), 7.16–7.75 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 17.83, 22.48, 28.93, 34.73, 47.19, 64. 04, 83.61, 85.17, 126.92, 127.26, 127.80, 128.79, 128.86, 129.04, 130.38, 136.55, 152.68, 160.39, 169.70. $C_{23}H_{24}N_2O_4$: calcd. C 70.39, H 6.16, N 7.14; found C 70.15, H 6.20, N 7.04.

l-**3b**: Colourless solid; m.p. 53.6–54.4°C; $[\alpha]_D^{28}$ = 88.7° (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 1.36 (3H, s, one of Me-5), 1.42 (3H, s, the other of Me-5), 1.49 (3H, d, *J* = 7.3 Hz, Me-4'), 2.88 (1H, dd, *J* = 14.2, 9.9 Hz, one of CH_2Ph), 3.27 (1H, dd, *J* = 14.2, 3.3 Hz, the other of CH_2Ph), 3.77 (1H, dq, *J* = 7.3, 2.6 Hz, H-4'), 3.84 (3H, s, OMe), 4.46 (1H, dd, *J* = 9.9, 3.3 Hz, H-4), 5.73 (1H, d, *J* = 2.6 Hz, H-5'), 6.92 (2H, d, *J* = 8.9 Hz, Ar), 7.18–7.31 (5H, m, Ph), 7.65 (2H, d, *J* = 8.9 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ = 17.88, 22.46, 28.91, 34.70, 47.46, 55.36, 64.02, 83.57, 84.96, 114.25, 120.23, 126.88, 128.77, 128.82, 129.02, 136.58, 152.68, 159.96, 161.22, 169.88. $C_{24}H_{26}N_2O_5$: calcd. C 68.23, H 6.20, N 6.63; found C 68.46, H 5.93, N 6.28.

l-**3c**: Colourless plates (from AcOEt–hexane); m.p. 126.8–127.5°C; $[\alpha]_D^{28}$ = 89.3° (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 1.37 (3H, s, one of Me-5), 1.43 (3H, s, the other of Me-5), 1.48 (3H, d, *J* = 7.3 Hz, Me-4'), 2.88 (1H, dd, *J* = 14.5, 9.9 Hz, one of CH_2Ph), 3.26 (1H, dd, *J* = 14.5, 3.3 Hz, the other of CH_2Ph), 3.78 (1H, dq, *J* = 7.3, 2.6 Hz, H-4'), 4.47 (1H, dd, *J* = 9.9, 3.3 Hz, H-4), 5.77 (1H, d, *J* = 2.6 Hz, H-5'), 7.17-7.31 (5H, m, Ph), 7.38 (2H, d, *J* = 8.6 Hz, Ar), 7.65 (2H, d, *J* = 8.6 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ = 17.72, 22.46, 28.91, 34.75, 46.92, 64.04, 83.65, 85.32, 126.32, 126.93, 128.50, 128.80, 129.02, 129.16, 136.39, 136.48, 152.65, 159.65, 159.55, 169.52. $C_{23}H_{23}ClN_2O_4$: calcd. C 64.71, H 5.43, N 6.56; found C 64.55, H 5.38, N 6.53.

l-**3d**: Colourless plates (from AcOEt–hexane); m.p. 144.5–145.1°C; $[\alpha]_D^{28}$ = 96.9° (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 1.37 (3H, s, one of Me-5), 1.43 (3H, s, the other of Me-5), 1.48 (3H, d, *J* = 6.9 Hz, Me-4'), 2.88 (1H, dd, *J* = 14.5, 9.9 Hz, one of CH_2Ph), 3.27 (1H, dd, *J* = 14.5, 3.6 Hz, the other of CH_2Ph), 3.79 (1H, dq, *J* = 6.9, 2.6 Hz, H-4'), 4.48 (1H, dd, *J* = 9.9, 3.6 Hz, H-4), 5.77 (1H, d, *J* = 2.6 Hz, H-5'), 7.08-7.31 (5H, m, Ph), 7.10 (2H, d, *J* = 8.9 Hz, Ar), 7.63 (2H, dd, *J* = 8.9, 5.3 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ = 17.72, 22.46, 28.91, 34.73, 47.12, 64.04, 83.63, 85.23, 116.05 (d, $J_{C\text{-}F}$ = 22.0 Hz), 124.06 (d, $J_{C\text{-}F}$ = 2.5 Hz),126.93, 128.80, 129.11 (d, $J_{C\text{-}F}$ = 8.3 Hz), 129.32, 136.51, 152.65, 159.49, 163.89 (d, $J_{C\text{-}F}$ = 250.2 Hz), 169.63. $C_{23}H_{23}FN_2O_4$: calcd. C 67.31, H 5.65, N 6.83; found C 67.13, H 5.59, N 6.78.

l-**3e**: Pale yellow plates (from AcOEt–hexane); m.p. 185.7–162.3°C; $[\alpha]_D^{28}$ = 126.2° (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 1.38 (3H, s, one of Me-5), 1.45 (3H, s, the other of Me-5), 1.50 (3H, d, *J* = 7.3 Hz, Me-4'), 2.90 (1H, dd, *J* = 14.2, 9.6 Hz, one of CH_2Ph), 3.27 (1H, dd, *J* = 14.2, 3.6 Hz, the other of CH_2Ph), 3.85 (1H, dq, *J* = 7.3, 3.0 Hz, H-4'), 4.48 (1H, dd, *J* = 9.6, 3.6 Hz, H-4), 5.85 (1H, d, *J* = 3.6 Hz, H-5'), 7.10–7.35 (5H, m, Ph), 7.89 (2H, d, *J* = 8.9 Hz, Ar), 8.27 (2H, d, *J* = 8.9 Hz, Ar). $C_{23}H_{23}N_3O_6$: calcd. C 63.15, H 5.30, N 9.61; found C 62.87, H 5.23, N 9.55.

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