Formation of 5-Alkoxy-2-aminooxazoles and Their Novel Reactivity: Equilibrium with Nitrile Ylide

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The $Rh_2(OAc)_4$-catalyzed reactions of diazoacetates with diisopropylcyanamide gave 5-alkoxy-2-aminooxazoles. Their isolation was achieved by introduction of a bulky alkoxy group at 5-position. The 5-alkoxy-2-aminooxazole reacted with methanol to give a 1 : 1-adduct in a quantitative yield. The kinetic study indicates that this reaction proceeds in a stepwise mechanism including an equilibrium of the 5-alkoxy-2-aminooxazole with a nitrile ylide intermediate.

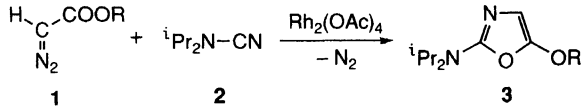
In recent years, oxazoles have been of increasing interest as useful reaction intermediates in syntheses of natural products.[1] Because of their low aromaticity, oxazoles are known to behave as 2-azadiene 4π systems. The Diels–Alder reaction is often used for the ring-transformation from oxazoles to pyridines or furans.[1] The abnormal Diels–Alder reaction, in which oxazoles behave as formal C–N–C 4π systems, is an alternative method for the ring-transformations giving pyrrolines, oxazolines, oxadiazolines, thiazolines, and triazolines.[2] In both types of reactions, electron-releasing substituents such as alkoxy and amino groups are required for activation of oxazoles.

In our previous paper, we reported a new synthetic method of 2-aminooxazoles under mild reaction conditions.[3] The reactions of α-diazoacetophenones with dialkylcyanamides are catalyzed by $Rh_2(OAc)_4$, which is superior to a Lewis acid catalyst such as BF_3-etherate, and gave 2-(dialkylamino)oxazoles in high yields. As an extension of this work, the reaction using $Rh_2(OAc)_4$ as a catalyst can be applied for the synthesis of 5-alkoxy-2-aminooxazoles which are expected to possess an increased reactivity owing to two electron-releasing groups.

In this paper, we wish to report the synthesis of 5-alkoxy-2-aminooxazoles by $Rh_2(OAc)_4$-catalyzed reactions of diazoacetates with dialkylcyanamides. The 5-alkoxy-2-aminooxazoles were labile and reacted with alcohol very easily. This high reactivity is attributed to its nature, that is, a heteroaromatic nucleus of the 5-alkoxy-2-aminooxazole opens easily and is in equilibrium with an acyl-substituted nitrile ylide.

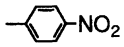
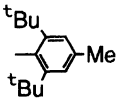
Results and Discussion

$Rh_2(OAc)_4$-catalyzed reactions of diazoacetate **1** with diisopropylcyanamide (**2**) giving the corresponding 5-alkoxy-2-(diisopropylamino)oxazole **3** are listed in Table 1. The reaction of ethyl diazoacetate (**1a**) with 10 molar amounts of cyanamide **2** in the presence of a 0.05 molar amount of



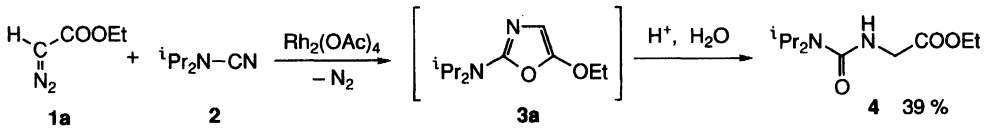
1 **2** **3**

Table 1. $Rh_2(OAc)_4$-Catalyzed Reaction of Diazoacetate **1** with Diisopropylcyanamide (**2**)

Run	R	Yield/%
a	Et	Not isolated[a]
b	^{i}Pr	Not isolated[a]
c	^{t}Bu	49[a]
d		33[a]
e		Not isolated[a]
f		25[a]

a) Almost quantitative formation of **3** was observed by NMR.

$Rh_2(OAc)_4$ gave a single raw product whose ^{1}H NMR spectrum indicated an almost quantitative formation of 2-(diisopropylamino)-5-ethoxyoxazole (**3a**). However, despite efforts for isolation such as column chromatography on silica gel or alumina and distillation under reduced pressure, **3a** decomposed or polymerized completely without isolation. Other information about the formation of **3a** was obtained by treatment of the reaction mixture with 6 M (1 M = 1 mol dm^{-3}) of aqueous solution of HCl to afford a urea derivative **4** (Scheme 1). For the isolation of **3**, we employed stabilization of **3** by introduction of a bulky substituent (Table 1). Although the reaction of the isopropyl diazoacetate **1b** (Run b) resulted in the same result as in the case of **1a**, the use of the *t*-alkyl diazoacetates **1c** and **1d** enabled the isolation of the corresponding oxazoles **3c** and **3d** in 49 and 33% yields, respectively (Table 1, Runs c and d). When aryl diazoacetates are used (Runs e and f), a similar



Scheme 1.

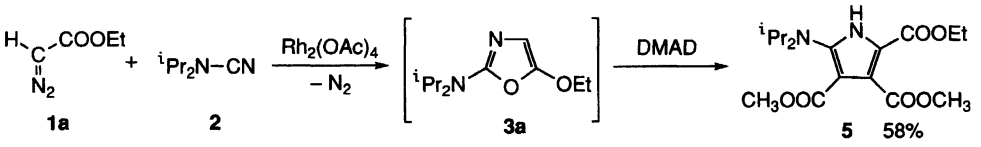
trend is observed, that is, only **3f**, having an extremely bulky substituent, shows stability to be isolated in a 25% yield.

In the previous paper, an unusual reactivity of 5-alkoxy-2-aminooxazole **3** was mentioned briefly.[3] The addition of dimethyl acetylenedicarboxylate (DMAD) into the reaction mixture of **1a** and **2** after complete decomposition of **1a** resulted in the predominant formation of dimethyl 2-(diisopropylamino)-5-(ethoxycarbonyl)pyrrole-3,4-dicarboxylate (**5**) (Scheme 2). According to the generally accepted reactivity of oxazoles toward acetylene derivatives, the formation of furan derivatives is expected through the elimination of HCN from the Diels–Alder adduct. Thus it is very hard to explain this reaction by a direct attack of oxazole **3** to DMAD, and the existence of some intermediate such as a nitrile ylide during the course of the reaction is anticipated.

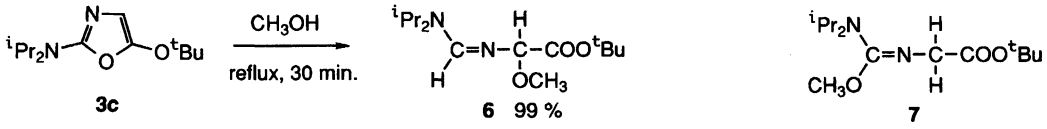
For the clarification of the reactivity of 5-alkoxy-2-aminooxazole **3**, the reaction of **3c** with methanol was carried out, and 1:1-product **6** was obtained in almost quantitative yield (Scheme 3). The spectroscopic data and elemental analysis clearly show that **6** is a 1:1-adduct of **3c** with methanol. The ^{13}C NMR signal at 169.63 ppm is assigned to a carbonyl carbon of an ester group generated by the opening of the oxazole ring. The open-chain structure of **6** is also supported by the strong absorption of ester carbonyl group at 1745 cm^{-1} in its IR spectrum. The regiochemistry of the addition of methanol is confirmed by ^{13}C NMR spectrum as follows; the observation of the two doublet signals at 152.76 and 94.99 ppm indicates the existence of a imine carbon and a methine carbon, and excludes the possibility of another structure **7** which is expected to be produced in a similar reaction as the acid-catalyzed hydrolysis of oxazole (Scheme 1).

There are two conceivable pathways in the reaction of **3c** with methanol to give **6** (Scheme 4). One includes a ring opening of **3c** to generate the nitrile ylide intermediate, followed by an addition of methanol (*path a*). The other is depicted as a direct reaction of the oxazole with methanol accompanying the ring opening of oxazole (*path b*).

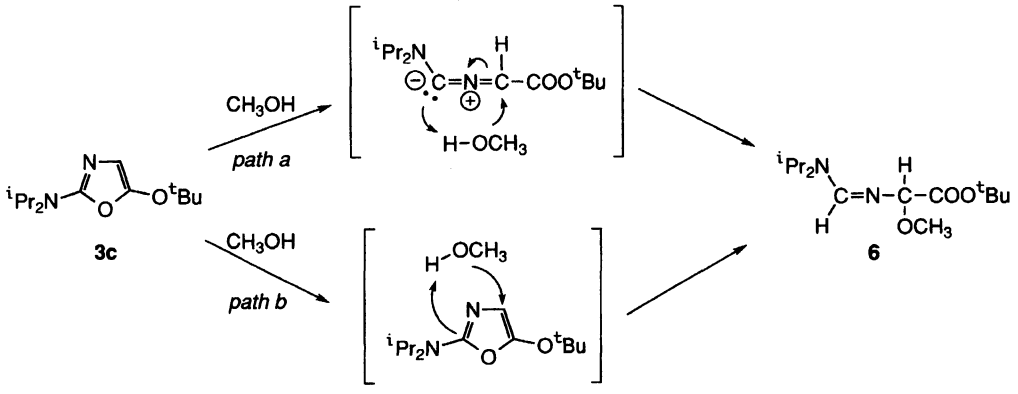
In order to determine the mechanism, a kinetic study of the reaction of **3c** with 1.2 molar amounts of methanol was carried out in C_6D_6 at 80±0.1°C and the decrease of **3c** was followed by ^{1}H NMR. The reaction obeyed the first-order kinetics ($r=0.997$, $k=4.36\times10^{-5}$s^{-1}) until 95% of **3c** was consumed. This implies that the reaction proceeds stepwise. The process can be explained by the following rate equation, obtained by assuming the nitrile ylide as an intermediate and treating a stationary state for the intermediate, $d[ny]/dt=0$



Scheme 2.



Scheme 3.



Scheme 4.

(where [ny] is the concentration of the nitrile ylide).

$$-\mathrm{d}[\mathbf{3c}]/\mathrm{d}t = k_1k_2[\mathbf{3c}][\mathrm{MeOH}]/(k_{-1}+k_2[\mathrm{MeOH}]). \quad (1)$$

When k_{-1} is much smaller than k_2[MeOH], k_{-1} can be neglected to give Eq. 2.

$$-\mathrm{d}[\mathbf{3c}]/\mathrm{d}t = k_1[\mathbf{3c}]. \quad (2)$$

Therefore, our result suggests that the formation of **6** proceeds through *path a*, and the oxazole **3c** is in equilibrium with the nitrile ylide intermediate under thermal conditions. Since methanol reacts with the nitrile ylide very fast ($k_2 \gg k_{-1}$), the ring opening of **3c** is the rate-determining step in the whole reaction pathway (Fig. 1) to give first-order kinetics.

In order to explain the activating effect of the amino group on the ring opening of the oxazole **3**, the MINDO/3 molecular orbital calculations[4] were carried out for the ring opening of the oxazoles having three sets of substituents (Fig. 2). The calculated heats of formation (H_f) are listed in Table 2. The introduction of an alkoxy group at the 5-position (Compd b) lowers the difference of the heat of formation ($\Delta H^{\neq}$) between the oxazole (**OX**) and the transition state (**TS**). The substitution of the amino group at the 2-position further decreases the value of $\Delta H^{\neq}$ (Compd c).

According to the MINDO/3 calculations, the optimized structures of these nitrile ylides (**NYa–NYc**) were found to have bent forms, of which the bond angles of N^4–C^5–R^1 are 123.3—126.0° (Table 3). In the structure of **NYc**, the length of N^4–C^5 (1.260 Å) is longer than those of **NYa** and **NYb** (1.198 and 1.203 Å, respectively). The bond order of N^4–C^5 (1.596) is decreased very much, and that of C^5–R^1 (C^5–N) (1.226) is increased in **NYc** in comparison to **NYa** and **NYb** (for N^4–C^5 2.206 and 2.154, and for C^5–R^1 (C^5–H) 0.866 and 0.868, respectively). These structural features indicate that the contribution of the resonance structure **B** is significant in the amino-substituted nitrile ylide **NYc**, which has a long N^4–C^5 bond and a short C^5–R^1 (C^5–N) bond. Therefore, we conclude that the introduction of the amino group on the nitrile carbon stabilizes the nitrile ylide, because it contributes to the delocalization of the positive charge on N^4 (Scheme 5).

As one example of the oxazole ring opening through the nitrile ylide intermediate, the Cornforth rearrangement has been extensively investigated by Dewar and Turchi.[5] In this reaction, an alkoxy group at 5-position and an electron-withdrawing group at 4-position are required to generate a diacyl-substituted nitrile ylide. Saalfrank et al. also reported a similar reaction; the treatment of 4-cyano-5-methoxy-2-(1-pyrrolidinyl)oxazole with methyl acrylate in toluene at 60 °C gave a pyrroline derivative through 1,3-dipolar cycloaddition of a nitrile ylide intermediate generated by the ring opening of the oxazole derivative.[6] In this case, introduc-

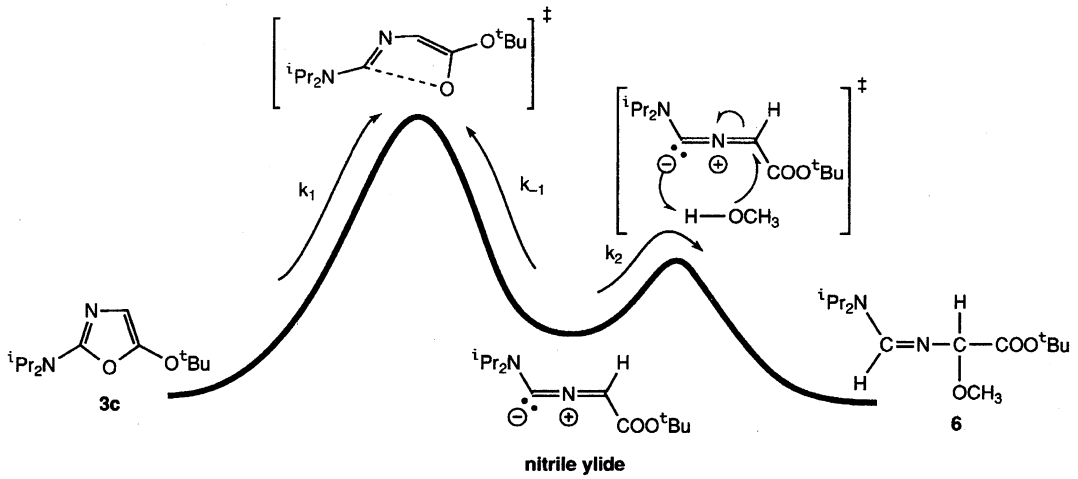


Fig. 1. Energy profile of reaction of **3c** with methanol.

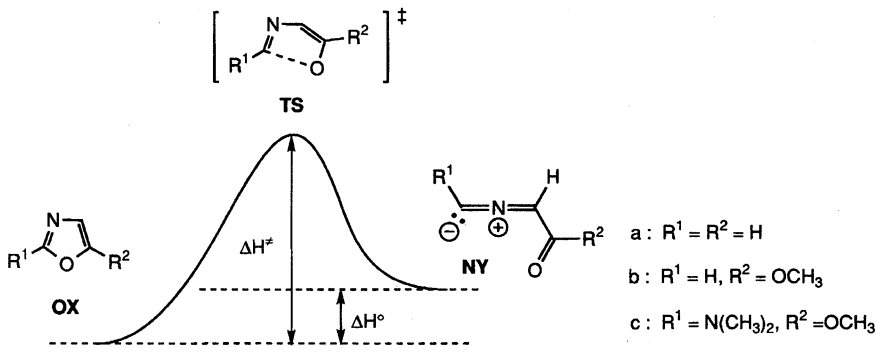


Fig. 2. Energy profile of ring opening of oxazole derivatives.

Table 2. Heats of Formation of Oxazole (**OX**), Transition State (**TS**), and Nitrile Ylide (**NY**) Calculated by MINDO/3

Compd	R^1	R^2	H_f/kcal mol^{-1}			$\Delta H^{\neq}$	$\Delta H°$
			OX	**TS**	**NY**	kcal mol^{-1}	kcal mol^{-1}
a	H	H	−7.42	35.54	2.80	42.96	10.22
b	H	OCH_3	−55.67	−19.77	−53.90	35.90	1.77
c	$N(CH_3)_2$	OCH_3	−55.10	−32.00	−63.24	23.10	−8.14

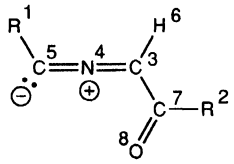
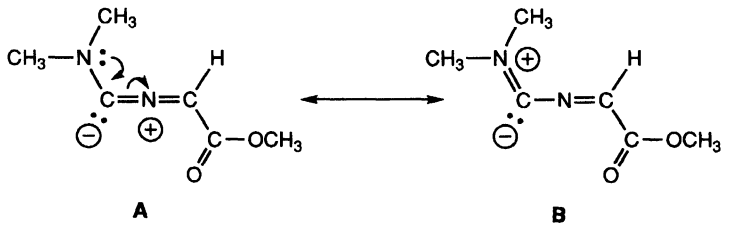


Table 3. Optimized Structure of Nitrile Ylide by MINDO/3 Calculation

Bond length (Å)	C^3–N^4	N^4–C^5	C^5–R^1	C^3–H^6	C^3–C^7	C^7–O^8	C^7–R^2
NYa	1.289	1.198	1.107 (C^5–H)	1.113	1.449	1.199	1.136 (C^7–H)
NYb	1.285	1.203	1.111 (C^5–H)	1.113	1.478	1.215	1.335 (C^7–O)
NYc	1.262	1.260	1.340 (C^5–N)	1.122	1.491	1.210	1.333 (C^7–O)
Bond order	C^3–N^4	N^4–C^5	C^5–R^1	C^3–H^6	C^3–C^7	C^7–O^8	C^7–R^2
NYa	1.476	2.206	0.866 (C^5–H)	0.917	0.995	1.750	0.844 (C^7–H)
NYb	1.527	2.154	0.868 (C^5–H)	0.915	0.931	1.624	0.905 (C^7–O)
NYc	1.741	1.596	1.226 (C^5–N)	0.892	0.866	1.671	0.907 (C^7–O)
Bond angle (°)	C^3–N^4–C^5	N^4–C^5–R^1	H^6–C^3–N^4	C^7–C^3–N^4	C^3–C^7–O^8	C^3–C^7–R^2	
NYa	168.8	126.0 (N^4–C^5–H)	116.4	125.1	128.7	109.6 (C^3–C^7–H)	
NYb	169.3	123.3 (N^4–C^5–H)	115.6	122.0	124.1	105.0 (C^3–C^7–O)	
NYc	168.4	124.2 (N^4–C^5–N)	119.7	124.6	125.0	102.9 (C^3–C^7–O)	



Scheme 5.

tion of the pyrrolidinyl group at 2-position facilitates the ring opening of oxazole and enables the trapping of the nitrile ylide intermediate by methyl acrylate.

Our findings show that the 5-alkoxy-2-aminooxazole, activated by two electron-releasing groups, is able to open under the mild conditions to produce the alkoxycarbonyl-substituted nitrile ylide intermediate. The activation by the amino group at 2-position renders an electron-withdrawing group at 4-position unnecessary for the ring opening of the 5-alkoxyoxazole.

Here the effect of the amino group is ascribed to the stabilization of the nitrile ylide intermediate, which also reduces the enthalpy of activation. We wish to mention now other two conceivable characteristics of the 5-alkoxy-2-aminooxazole. One is the destabilization of the oxazole nucleus by two electron-donating groups, which raise the heat of formation of the oxazole derivative so the activation energy would become relatively low. The other one is the stabilization of the transition state from the oxazole to the nitrile ylide intermediate. That is, the breaking O–C bond becomes more polar in the transition state, and the positive charge developed on 2-position can be stabilized by the amino group effectively.

In conclusion, we provide 5-alkoxy-2-aminooxazoles as a new type of oxazole derivative by the $Rh_2(OAc)_4$-catalyzed reaction of diazoacetates with diisopropylcyanamide. Their lability is overcome by the introduction of the bulky substituent at 5-position. Furthermore, these oxazole derivatives are found to be in equilibrium with the nitrile ylide intermediate. Therefore, the 5-alkoxy-2-aminooxazole is regarded as an synthetic equivalent of the alkoxycarbonyl-substituted nitrile ylide intermediate, with a smooth conversion under mild conditions. The reaction of the 5-alkoxy-2-aminooxazole with some dipolarophiles to give 5-membered heterocycles through 1,3-dipolar cycloaddition of the

alkoxycarbonyl-substituted nitrile ylide is now in progress.

Experimental

Melting points were measured with a Yanagimoto Melting-point Apparatus and were not corrected. IR spectra were recorded on a Perkin–Elmer model 983. ^{1}H NMR (270.05 MHz) and ^{13}C NMR (67.8 MHz) spectra were recorded on a JEOL EX-270 in a $CDCl_3$ solution using TMS as an internal standard. Mass spectra were determined with a JEOL JMS-DX303 spectrometer, and a Shimadzu GCMS-QP2000A gas chromatograph mass spectrometer. Elemental analyses were performed on a Yanaco CHN corder MT-5.

Materials and Solvents. Ethyl diazoacetate was prepared by the diazotization of glycine ethyl ester hydrochloride with sodium nitrite.[7] Isopropyl diazoacetate, *t*-butyl diazoacetate,[8] 1-Adamantyl diazoacetate, and 2,6-di-*t*-butyl-4-methylphenyl diazoacetate[9] were prepared by acyl cleavage of the corresponding α-diazoacetoacetates with sodium methoxide or potassium hydroxide. Methanol and DMAD were purified by distillation of the commercial reagent.

Ethyl (3,3-Diisopropylureido)acetate (4): A solution of 0.5 mmol of ethyl diazoacetate (**1a**) dissolved in 10 ml of benzene was added to a solution of 0.025 mmol of $Rh_2(OAc)_4$ and 5 mmol of diisopropylcyanamide (**2**) in 5 ml of benzene at 80 °C under Ar atmosphere for 2 h. Then the reaction mixture was stirred for 1 h to complete the reaction. The reaction mixture was washed with three portions of 10 ml of 6 M HCl. The combined aqueous layer was neutralized with sodium hydrogencarbonate, and was extracted with three portions of 10 ml of ether. The combined ethereal solution was dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure to give ethyl (3,3-diisopropylureido)acetate (**4**) in a 39% yield. Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.27 (12H, d, J=6.9 Hz, CH_3 of *i*-Pr), 1.29 (3H, t, J=7.3 Hz, CH_3 of Et), 3.92 (2H, spt, J=6.9 Hz, CH of *i*-Pr), 4.04 (2H, d, J=4.3 Hz, CH_2), 4.21 (2H, q, J=7.3 Hz, CH_2 of Et), 4.79 (1H, brs, NH); IR (neat) 3365 (NH), 2969, 1735 (C=O of ester), 1628 (C=O of urea), 1521, 1424, 1373, 1334, 1210, 1030, 861, and 767 cm^{-1}.

Measurement of ^{1}H NMR Spectrum of 2-Diisopropylamino-5-ethoxyoxazole (3a) in Reaction Mixture: A solution of 0.5 mmol of ethyl diazoacetate (**1a**) disolved in 2 ml of benzene was added to a mixture of 0.005 mmol of $Rh_2(OAc)_4$ and 2.5 mmol of diisopropylcyanamide (**2**) at 80 °C under Ar atmosphere for 20 min; then the reaction mixture was stirred for 1 h to complete the reaction. The ^{1}H NMR signals from the reaction mixture indicated the almost quantitative formation of 2-diisopropylamino-5-ethoxyoxazole (**3a**): ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.38 (3H, t, J=7.3 Hz, CH_3 of Et), 3.94 (2H, spt, J=6.9 Hz, CH), 4.03 (2H, q, J=7.3 Hz, CH_2), 5.82 (1H, s, 4-H). The signal of CH_3 of *i*-Pr was hidden in the signal of excess of diisopropylcyanamide. The attempts to isolate **3a** using column chromatography on silica gel or alumina and distillation were unsuccessful.

Measurement of ^{1}H NMR Spectrum of 2-Diisopropylamino-5-isopropoxyoxazole (3b) in Reaction Mixture: A solution of 0.5 mmol of isopropyl diazoacetate (**1b**) dissolved in 2 ml of benzene was added to a mixture of 0.005 mmol of $Rh_2(OAc)_4$ and 2.5 mmol of diisopropylcyanamide (**2**) at 80 °C under Ar atmosphere for 20 min; then the reaction mixture was stirred for 1 h to complete the reaction. The ^{1}H NMR signals of the reaction mixture indicated the almost quantitative formation of 2-diisopropylamino-5-isopropyloxyoxazole (**3b**): ^{1}H NMR (270 MHz, $CDCl_3$) δ=3.95 (2H, m, CH of NPr^i_2), 4.26 (2H, m, CH of OPr^i), 5.90 (1H, s, 4-H). The signals of CH_3 of *i*-Pr's were hidden in the signal of excess of diisopropylcyanamide. The isolation of **3b** using silica-gel column chromatography was unsuccessful.

5-*t*-Butoxy-2-(diisopropylamino)oxazole (3c): A solution of 0.5 mmol of *t*-butyl diazoacetate (**1c**) dissolved in 2 ml of benzene was added to a mixture of 0.005 mmol of $Rh_2(OAc)_4$ and 2.5 mmol of diisopropylcyanamide (**2**) at 80 °C under Ar atmosphere for 20 min; then the reaction mixture was stirred for 1 h to complete the reaction. After removal of solvent and excess dissopropylcyanamide (**2**) under reduced pressure, distillation of the residual oil with Kugelrohr gave 5-*t*-butoxy-2-(diisopropylamino)oxazole (**3c**) in a 49% yield. Colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.26 (12H, d, J=6.9 Hz, CH_3 of *i*-Pr), 1.35 (9H, s, CH_3 of *t*-Bu), 3.97 (2H, spt, J=6.9 Hz, CH), 5.99 (1H, s, 4-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.01 (qqui, $^2J_{CH}$, $^3J_{CH}$=4.3 Hz, CH_3 of *i*-Pr), 28.04 (qspt, $^3J_{CH}$=3.7 Hz, CH_3 of *t*-Bu), 46.50 (dsxt, $^2J_{CH}$=4.3 Hz, CH), 82.31 (quaternary-C of *t*-Bu), 107.41 (d, J_{CH}=191.7 Hz, 4-CH), 150.11 (sd, $^2J_{CH}$=13.4 Hz, 5-C), 155.20 (dt, $^3J_{CH}$=11.6 and 6.1 Hz, 2-C); IR (neat) 3124, 2973, 2932, 2832, 1730 (w), 1647, 1585 (C=N), 1455, 1420, 1389, 1367, 1327, 1266, 1227, 1207, 1150, 1130, 1035, 985, 963, 910, 853, 796, 775, 740, and 710 cm^{-1}. HRMS (EI, M$^+$) Found: *m/z* 240.1841. Calcd for $C_{13}H_{24}N_2O_2$: M, 240.1838.

1-Adamantyl Acetoacetate: To a solution of 5 mmol of 1-adamantanol and 0.26 mmol of sodium acetate dissolved in 3 ml of butyronitrile, 5 mmol of diketene was added dropwise for 30 min at reflux temperature under argon atmosphere. After 2 h heating of the reaction mixture, the butyronitrile was removed under reduced pressure. The residual oil was separated by silica-gel column chromatography eluted with ethyl acetate–hexane to give 1-adamantyl acetoacetate as a mixture of keto-form and enol-form (93 : 7) in an 86% yield. Yellow oil; ^{1}H NMR (240 MHz, $CDCl_3$) δ=1.60—1.75 (6H, m, CH_2 of adamantyl group), 1.91 (0.2H, s, CH_3 of enol-form), 2.05—2.23 (9H, m, CH_2 and CH of adamantyl group), 2.26 (2.8H, s, CH_3 of keto-form), 3.35 (1.85H, s, CH_2 of keto-form), 4.89 (0.07H, s, vinyl H of enol-form), 12.23 (0.07H, s, OH of enol-form); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.15 (CH_3 of enol-form), 30.00 (q, CH_3), 30.84 (d, CH of adamantyl group), 36.09 (t, CH_2 of adamantyl group), 41.19 (t, CH_2 of adamantyl group), 51.71 (t, CH_2), 80.81 (quaternary C of adamantyl group in enol form), 82.08 (s, quaternary C of adamantyl group), 91.04 (C=CH of enol-form), 166.08 (st, $^2J_{CH}$=7.3 Hz, C=O of ester group), 172.45 (C=O of ester group in enol-form), 174.71 (HO–C=CH of enol-form), 201.21 (ssxt, $^2J_{CH}$=6.1 Hz, C=O of keto group); IR (neat) 3427 (OH), 2910, 2852, 1735 (C=O), 1714 (C=O), 1645, 1453, 1410, 1355, 1325, 1298, 1241, 1186, 1152, 1103, 1056, 995, 968, 951, 934, 880, 814, 775, and 734 cm^{-1}.

1-Adamantyl Diazoacetate: To a solution of 5 mmol of 1-adamantyl acetoacetate and 5 mmol of potassium carbonate dissolved in 5 ml of acetonitrile, a solution of 5 mmol of *p*-toluenesulfonyl azide dissolved in 4 ml of acetonitrile was added dropwise for 15 min at room temperature. After 1 h stirring at room temperature, 10 ml of aqueous solution of 8% potassium hydroxide was added in one portion, and the reaction mixture was stirred overnight at room temperature. To the reaction mixture, 10 ml of water and 10 ml of ether were added, and the solution was separated with a separatory funnel. The aqueous layer was extracted with 2 portions of 10 ml of ether, and the combined organic solution was dried over anhydrous sodium sulfate. After removal of ether, 1-adamantyl diazoacetate was obtained in a 64% yield. Pale yellow solid; mp 61.3—63.0 °C (from ethyl acetate–hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.62—1.72 (9H, m, CH_2 and CH of adamantyl group), 2.10—2.24 (6H, m, CH_2 of adamantyl group), 4.60 (1H, s, H–C=N_2); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=30.92 (d,

CH of adamantyl group), 36.15 (t, CH_2 of adamantyl group), 41.66 (t, CH_2 of adamantyl group), 46.71 (d, H–C=N_2), 81.53 (s, quaternary C of adamantyl group), 165.90 (s, C=O); IR (neat) 3335, 3100, 2979, 2968, 2913, 2892, 2869, 2845, 2121 (C=N_2), 1683 (C=O), 1453, 1435, 1388, 1354, 1344, 1320, 1305, 1279, 1240, 1193, 1184, 1112, 1098, 1059, 1045, 1005, 995, 975, 938, 898, 818, 777, and 754 cm^{-1}. Found: C, 65.29; H, 7.27; N, 12.56%. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72 %.

5-(1-Adamantyloxy)-2-(diisopropylamino)oxazole (3d): A solution of 0.5 mmol of 1-adamantyl diazoacetate dissolved in 2 ml of benzene was added to a mixture of 0.005 mmol of $Rh_2(OAc)_4$ and 2.5 mmol of diisopropylcyanamide (**2**) at 80 °C under Ar atmosphere for 20 min, then the reaction mixture was stirred for 1 h to complete the reaction. After removal of solvent and excess diisopropylcyanamide (**2**) under reduced pressure, separation of the residual oil by column chromatography eluted with ethyl acetate-hexane gave 5-(1-adamantyloxy)-2-(diisopropylamino)oxazole (**3d**) in a 33% yield; pale yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.26 (12H, d, J=6.9 Hz, CH_3 of ^{i}Pr), 1.56—1.67 (6H, d, CH_2 of adamantyl group), 1.87 (6H, d, J=3.0 Hz, CH_2 of adamantyl group), 2.08—2.26 (3H, m, CH of adamantyl group), 3.97 (2H, spt, J=6.9 Hz, CH of ^{i}Pr), 5.97 (1H, s, 4-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.02 (qqui, $^2J_{CH}$, $^3J_{CH}$=4.3 Hz, CH_3 of ^{i}Pr), 30.99 (dm, CH of adamantyl group), 35.97 (tm, CH_2 of adamantyl group), 41.83 (tm, CH_2 of adamantyl group), 46.49 (dsxt, $^2J_{CH}$=4.3 Hz, CH of ^{i}Pr), 81.32 (sm, quaternary-C of adamantyl group), 107.46 (d, J_{CH}=192.3 Hz, 4-CH), 149.17 (sd, $^2J_{CH}$=14.0 Hz, 5-C), 155.20 (dt, $^3J_{CH}$=11.6 and 6.1 Hz, 2-C); IR (neat) 3119, 2968, 2911, 2851, 2679, 1780 (w), 1729 (w), 1647, 1577 (C=N), 1451, 1421, 1366, 1353, 1327, 1304, 1273, 1254, 1221, 1203, 1177, 1160, 1128, 1053, 1035, 986, 897, 862, 815, 795, and 734 cm^{-1}. HRMS (EI, M^+) Found: *m/z* 318.2309. Calcd for $C_{19}H_{30}N_2O_2$: M, 318.2307.

5-(2,6-Di-*t*-butyl-4-methylphenoxy)-2-(diisopropylamino)oxazole (3f): A solution of 1 mmol of 2,6-di-*t*-butyl-4-methylphenyl diazoacetate dissolved in 4 ml of benzene was added to a mixture of 0.05 mmol of $Rh_2(OAc)_4$ and 5 mmol of diisopropylcyanamide (**2**) at 80 °C under Ar atmosphere for 20 min, then the reaction mixture was stirred for 30 min to complete the reaction. After removal of solvent and an excess diisopropylcyanamide (**2**) under reduced pressure, 5-(2,6-di-*t*-butyl-4-methylphenoxy)-2-(diisopropylamino)oxazole was obtained by recrystallization from hexane in a 25% yield. Colorless crystals; mp 89.1—91.9 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.23 (12H, d, J=6.9 Hz, CH_3 of *i*-Pr), 1.33 (18H, s, CH_3 of *t*-Bu), 2.33 (3H, s, CH_3), 3.89 (2H, spt, J=6.9 Hz, CH of *i*-Pr), 5.23 (1H, s, 4-H), 7.09 (2H, s, H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.28 (qsxt, $^2J_{CH}$, $^3J_{CH}$=4.3 Hz, CH_3 of *i*-Pr), 21.74 (qt, $^2J_{CH}$=4.6 Hz, CH_3), 32.05 (qsxt, $^2J_{CH}$=4.9 Hz, CH_3 of *t*-Bu), 36.00 (sm, quaternary-C of *t*-Bu), 47.15 (dsxt, $^2J_{CH}$=4.3 Hz, CH of *i*-Pr), 98.56 (d, J_{CH}=195.9 Hz, 4-CH), 127.73 (d, CH of Ar), 134.46 (sq, $^2J_{CH}$=5.8 Hz, 4′-C of Ar), 143.03 (s, 2′ and 6′-C of Ar), 149.84 (st, $^2J_{CH}$=10.4 Hz, 1′-C of Ar), 153.28 (dt, $^3J_{CH}$=11.6 and 5.1 Hz, 2-C), 155.54 (sd, $^2J_{CH}$=12.8 Hz, 5-C); IR (KBr) 2968, 1656, 1589 (C=N), 1420, 1366, 1262, 1240, 1210, 1162, 1098, 910, 859, 817, 759, and 717 cm^{-1}. Found: C, 74.74; H, 9.96; N, 7.22%. Calcd for $C_{24}H_{38}N_2O_2$: C, 74.57; H, 9.91; N, 7.25%.

A solution of 0.1 mmol of 5-*t*-butoxy-2-(diisopropylamino)oxazole (**3c**) in 3 ml of methanol was heated at reflux temperature for 30 min. After removal of excess methanol, N^1,N^1-diisopropyl-N^2-[(*t*-butoxycarbonyl)methoxymethyl]formamidine (**6**) was obtained.

N^1,N^1-Diisopropyl-N^2-[(*t*-butoxycarbonyl)methoxymethyl]-formamidine (6): 99% yield; yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.20 (12H, brd, J=5.6 Hz, CH_3 of *i*-Pr), 1.47 (9H, s, CH_3 of *t*-Bu), 3.34 (3H, s, OCH_3), 4.56 (1H, s, CH), 7.65 (1H, s, N=CH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=19.83 (brq, CH_3 of *i*-Pr), 23.90 (brq, CH_3 of *i*-Pr), 28.02 (qqui, $^3J_{CH}$=4.3 Hz, CH_3 of *t*-Bu), 45.38 (dm, CH of *i*-Pr), 54.50 (qd, $^3J_{CH}$=3.7 Hz, OCH_3), 81.09 (sxt, $^2J_{CH}$=4.3 Hz, quaternary-C of *t*-Bu), 94.99 (dm, CH), 152.76 (ddt, J=166.6 Hz, $^3J_{CH}$=8.6 and 4.3 Hz, N=CH), 169.63 (s, COO*t*-Bu); IR (neat) 2969, 2820, 1745 (C=O), 1628 (C=N), 1460, 1440, 1391, 1367, 1290, 1213, 1155, 1109, 1175, 1010, 950, 846, and 806 cm^{-1}. HRMS (CI, M^++1) Found: *m/z* 273.2172. Calcd for $C_{14}H_{28}N_2O_3$: M, 273.2178.

Kinetic Studies. A solution of 36 mg (0.15 mmol) of 5-*t*-butoxy-2-(diisopropylamino)oxazole (**3c**) and 1.2 molar amounts of methanol dissolved in 1 ml of benzene-d_6 was heated in a sealed NMR tube in a thermostatically controlled silicone bath at 80 °C. The decrease of **3c** was monitored by ^{1}H NMR spectroscopy using H-4 (δ=5.99) of **3c** as a probe. The logarithms of the concentration of **3c** were plotted as a function of time, and the rate constant was estimated by the least squares method.

Molecular Orbital Calculations: The molecular orbital calculations were carried out using MINDO/3 Hamiltonian in MOPAC ver. 6.20 for Macintosh.[10] The structures of oxazoles and nitrile ylides were optimized by the eigenvector-following method (EF). The MINDO/3 hamiltonian gave a bent form as an optimized structure for each nitrile ylide. The structures of the transition state were obtained by "SADDLE", and optimized by the eigenvector-following method (TS). The force calculation of each optimized structure in transition state gave only one imaginary frequency, and its direction was along C–O bond.

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