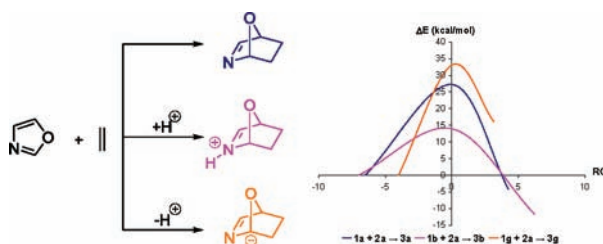


Oxazole as an Electron-Deficient Diene in
the Diels–Alder ReactionGaldina Vanessa Suárez-Moreno, Eduardo González-Zamora, and
Francisco Méndez**Departamento de Química, División de Ciencias Básicas e Ingeniería,
Universidad Autónoma Metropolitana-Iztapalapa, A.P. 55-534, México,
D.F. 09340, Mexico*

fm@xanum.uam.mx

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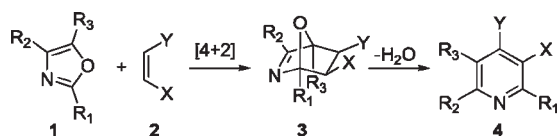
ABSTRACT



The Diels–Alder cycloaddition reaction of oxazole with ethylene is facilitated by addition of an alkyl group or Brønsted or Lewis acids to the oxazole nitrogen atom. The efficacy consists of stabilizing the transition state, lowering the activation barrier and the HOMO(dienophile)–LUMO(diene) gap, and increasing the reaction exothermicity.

The Diels–Alder reactions of oxazoles (**1**) and alkenes (**2**), with a subsequent dehydration of the cycloadducts (**3**), are becoming a mainstay of substituted pyridines (**4**) and synthesis of natural products such as vitamin B₆ and its analogues, which are accessible only with difficulty through other routes (Scheme 1).¹

Scheme 1



(1) Vitamin B₆ is the generic descriptor for 3-hydroxy-2-methylpyridine derivatives. It is an important nutrient and plays an essential role in the body's amino acid biochemical pathways. The preferred synthesis of vitamin B₆ uses the Diels–Alder reaction of **1** and **2**. See: (a) Kondrat'eva, G. Y. *Khim. Nauk Prom.* **1957**, 2, 666. (b) Firestone, R. A.; Harris, E. E.; Reuter, W. *Tetrahedron* **1967**, 23, 943. (c) Pauling, H.; Weimann, B. J. Vitamin B₆. In *Ullmann's Encyclopedia of Industrial Chemistry*; VCH: Weinheim, 1966; Vol. A27, p 530. (d) Doktorova, N. D.; Ionova, L. V.; Karpeisky, M. YA.; Padyukova, N. SH.; Turchin, K. F.; Florientev, V. L. *Tetrahedron* **1969**, 25, 3527. (e) Dumond, Y. R.; Gum, A. G. *Molecules* **2003**, 8, 873.

Although the inverse-electron-demand Diels–Alder (IEDDA) reaction of **1** and **2** ought to be an efficient method for the preparation of **4** (via the aromatization of cycloadduct **3**), the advance of the oxazole Diels–Alder reaction to the status of a general synthetic method owes much to the development of methods to activate the oxazole ring toward cycloaddition due to its intrinsically electron-deficient nature.² Therefore, the normal electron-demand Diels–Alder (NEDDA) reaction is the more commonly employed method, using electron-rich **1** and electron-poor **2**.³ However, interest in the IEDDA reaction, using

(2) Boger, D. *Chem. Rev.* **1986**, 86, 781 and references cited therein.

(3) (a) Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley: Weinheim, 2005. (b) Dömling, A. *Chem. Rev.* **2006**, 106, 17. (c) Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, 3, 877. (d) González-Zamora, E.; Fayol, A.; Bois-Choussy, M.; Chiaroni, A.; Zhu, J. *Chem. Commun.* **2001**, 1684. (e) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, 75, 389. (f) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, 124, 2560. (g) Fayol, A.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, 41, 3633.

(4) (a) Doktorova, N. D.; Ionova, L. V.; Karpeisky, M. Y.; Padyukova, N. S.; Turchin, K. F.; Florentiev, V. L. *Tetrahedron* **1969**, 25, 3527. (b) Vasil'ev, N. V.; Koselev, V. M.; Romanov, D. V.; Lyssenko, K. A.; Antipin, M. Y.; Zatonskii, G. V. *Russ. Chem. Bull., Int. Ed.* **2005**, 54, 1680.

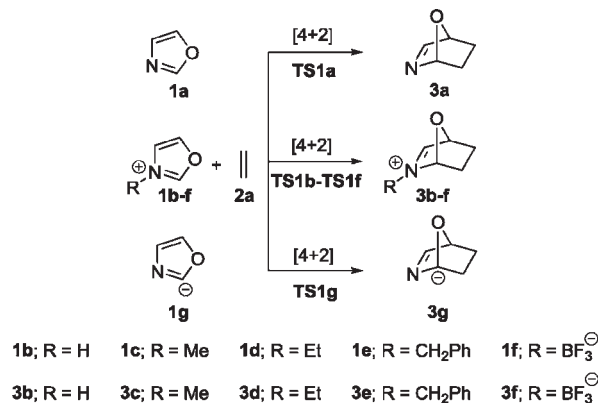
(5) (a) González, J.; Taylor, E. C.; Houk, K. N. *J. Org. Chem.* **1992**, 57, 3753. (b) Jursic, B. S.; Zdravkovski, Z. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1877. (c) Jursic, B. S. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1021.

electron-poor **1** and electron-rich **2**, remains unabated (from both experimental^{2,4} and theoretical⁵ points of view) because of the harsh conditions and high temperatures of the NEDDA reaction.^{1b,6} In contrast, the successful inverse-electron-demand azadiene-Diels–Alder (IEDADA) strategy used by a number of researchers has facilitated the azadiene Diels–Alder reaction by introducing electron-withdrawing substituents to the nitrogen atom of azadiene⁷ or the Brønsted and Lewis acid-catalyzed IEDADA reaction of azadiene to increase its activity with a selected dienophile.⁸ Therefore, in analogy with the IEDADA, we consider that the key to realizing the potential of the oxazole IEDDA reaction should be increasing its electron-deficient nature by adding an alkyl group or Brønsted or Lewis acids to the nitrogen atom of the ring. Our aim in this work is to establish theoretically the global reactivity diagram for the IEDDA and NEDDA reactions of **1** and **2** and clarify the role of the electron-rich, electron-poor, and neutral structures of **1** in both processes. This paper gives a discussion of the kinetic and thermodynamic properties of the IEDDA and NEDDA reactions between oxazole (**1a**), its electron-poor oxazolium cations (**1b–f**), and its electron-rich oxazolium anion (**1g**) with ethylene (**2a**) to obtain the Diels–Alder cycloadducts **3a**, **3b–f**, and **3g**, respectively (Scheme 2). We have found that the oxazolium cations **1b–f** accelerate the IEDDA reaction rates, making the process substantially exothermic, while the oxazolium anion (**1g**) decelerates the NEDDA reaction rates, making the process substantially endothermic. The efficacy of the oxazolium cations (**1b–f**) versus the neutral (**1a**) and anion (**1g**) analogous similarly decreases the HOMO–LUMO gap and stabilizes the transition state.

Molecular orbital calculations (SCF-MO and KS-MO)⁹ were carried out using GAUSSIAN03¹⁰ to study the cycloaddition reactions between **1a**, **1b–f**, and **1g** with **2a** to obtain the corresponding Diels–Alder cycloadducts **3a**,

3b–f, and **3g** and their transition states **TS1a**, **TS1b–f**, and **TS1g**, respectively (Scheme 2). In general, the results obtained with the SCF-MO and KS-MO calculations followed the same trend,¹¹ and they are summarized in Tables S1–S4 in the Supporting Information.

Scheme 2



The reaction mechanisms that lead to the Diels–Alder cycloadducts, **3a**, **3b–f**, and **3g** were investigated through IRC analyses¹² starting from the TSs already located (see Figure 1). The analyses performed led to the Diels–Alder cycloadducts in the forward direction and the reagents in the reverse direction without evidence of any intermediates/complexes structures along the reaction paths (Figures 2 and 3).

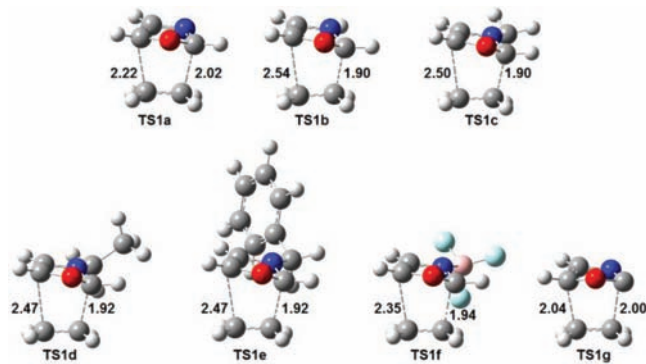


Figure 1. Transition structures obtained at the B3LYP/6-311+G(2d,2p) level of theory.

In general, the degree of asynchronicity¹³ for the TSs follows the trend $\Delta r_{\text{TS1b}} > \Delta r_{\text{TS1c}} > \Delta r_{\text{TS1d}} > \Delta r_{\text{TS1e}} > \Delta r_{\text{TS1f}} > \Delta r_{\text{TS1a}} > \Delta r_{\text{TS1g}}$. In all TSs, the C₂(oxazole)–C(ethylene) bond is shorter than the C₅(oxazole)–C(ethylene)

(6) See, for example: (a) Zamudio-Medina, A.; García-González, M. C.; Padilla, J.; González-Zamora, E. *Tetrahedron Lett.* **2010**, *51*, 4837. (b) Ducept, P. C.; Marsden, S. P. *ARKIVOC* **2002**, *v(i)*, 24. (c) Dumond, Y. R.; Gum, A. G. *Molecules* **2003**, *8*, 873. (d) Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35*, 1441.

(7) The introduction of electron-donor groups to the imine nitrogen of 1-azadiene or 2-azadiene reverses the natural electron-deficient character of the azadiene. Sufficient donation raises the HOMO of the azadiene and causes the reaction to proceed through the normal HOMO-controlled manifold. See: Buonara, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.

(8) (a) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259. (b) Buonara, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2000**, *57*, 6099. (c) Jayakumar, S.; Ishaar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379. (d) Cao, J.; Yang, X.; Hua, X.; Deng, Y.; Lai, G. *Org. Lett.* **2011**, *13*, 478. (e) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (f) Palacios, F.; Alonso, C.; Arrieta, A.; Cossio, F. P.; Ezpeleta, J. M.; Fuentes, M.; Rubiales, G. *Eur. J. Org. Chem.* **2010**, *11*, 2091. (g) Xie, M.; Chen, X.; Zhu, Y.; Gao, B.; Lin, L.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799. (h) Ding, Y.-Q.; Fang, D.-C. *J. Org. Chem.* **2010**, *11*, 2091. (i) Dagoussset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804.

(9) Calculations at the HF/6-31+G(d,p), HF/6-311+G(2d,2p), HF/AUG-cc-pVDZ, MP2/6-31+G(d,p), MP2/6-311+G(2d,2p), MP2/AUG-cc-pVDZ, CBS-QB3, B3LYP/6-31+G(d,p), B3LYP/6-311+G(2d,2p), BHandHLYP/6-31+G(d,p), BHandHLYP/6-311+G(2d,2p), and BHandHLYP/AUG-cc-pVDZ levels were carried out.

(10) Frisch, M. J. et al. Gaussian 03, Revision C.02; Gaussian, Inc., Wallingford, CT, 2004. The full reference is provided in the Supporting Information.

(11) For a discussion of eigenvalues, see, for example: Stowasser, R.; Hoffmann, R. *J. Am. Chem. Soc.* **1999**, *121*, 3414.

(12) (a) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161. (b) Ishida, K.; Morokuma, K.; Komornicki, A. *J. Chem. Phys.* **1977**, *66*, 2153.

(13) $\Delta r_{\text{TS}} = r_{[\text{C}_2(\text{oxazole})-\text{C}(\text{ethylene})]} - r_{[\text{C}_5(\text{oxazole})-\text{C}(\text{ethylene})]}$ (see Table S1 in the Supporting Information).

bond, except for **TS1g** where both bonds are similar ($\Delta r_{\text{TS1g}} = 0.02, 0.04, \text{ and } 0.05 \text{ \AA}$ for CBS-QB3/6-31+(d,p), B3LYP/6-311+G(2d,2p), and MP2/AUG-cc-pVDZ levels, respectively). Thus, **TS1b**, **TS1c**, **TS1d**, **TS1e**, **TS1f**, and **TS1a** correspond to concerted asynchronous reaction pathways, and **TS1g** correspond, to a concerted synchronous reaction path. The normal mode imaginary frequency ν in the TS reflects the asynchronous changes in geometry in going from reactants to products; $\nu = 318.22\Delta r_{\text{TS}} - 598.84$ ($R^2 = 0.92$).¹⁴

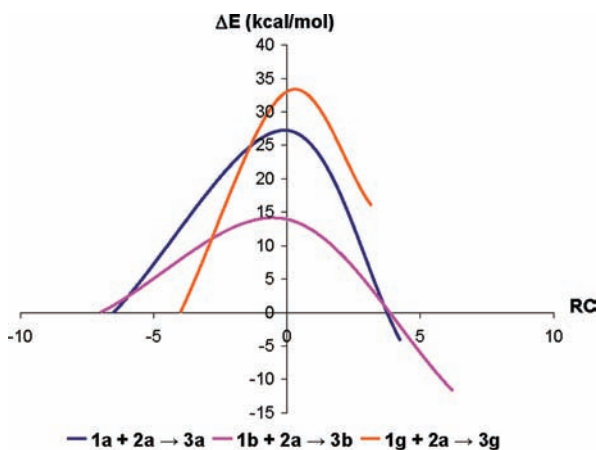


Figure 2. Plots of the IRC (in bohr/amu^{1/2}) versus energy (kcal/mol, relative to diene + **2a**) starting from the **TS1a**, **TS1b**, and **TS1g** computed at the B3LYP/6-311+G(2d,2p) level of theory.

In Figures 2 and 3 we can observe that the easiest reactions, in terms of activation energy, are those involving the coupling of the electron-poor oxazolium cations **1b**, **1c**, **1d**, **1e**, and **1f** with **2a**. The reaction of the neutral oxazole **1a** is less easy than the oxazolium cation **1b**, by about 10–14 kcal/mol, whereas the reaction of the oxazolium anion **1g** suffers from a very large penalty of 15–20 kcal/mol (see Tables S1 and S3 in the Supporting Information). Not only is the activation energy high, but the reaction of **1g** with **2a** is endothermic. The reactions of **1b–f** with **2a** are quite exothermic, with a heat of reaction about 5–8 and 26–35 kcal/mol lower than the reactions of **1a** and **1g** with **2a**, respectively.¹⁵ Even considering the unfavorable entropy for all these bimolecular reactions, by about $T\Delta S^\circ = -14$ kcal/mol, the highly exothermic reactions between the electron-poor oxazolium cations **1b–f** with **2a** have favorable free energies. On the other hand, the free energy of the neutral oxazole, **1a**, and oxazolium anion, **1g**, reaction will be unfavorable by about 5–8 and 26–35 kcal/mol, respectively (see Tables S2 and S4 in the Supporting Information).

Table 1 reports the eigenvalues of the HOMO and LUMO orbitals for **1a**, **2a**, **1b–f**, and **1g** obtained at the

(14) The ν and Δr_{TS} values were obtained at the B3LYP/6-311+G(2d,2p) level of theory.

(15) Our calculated E_a and $\Delta E(\text{rxn})$ values for **1a/2a** and **1b/2a** reactions match very well with those obtained by Houk and Jursic; see ref 5.

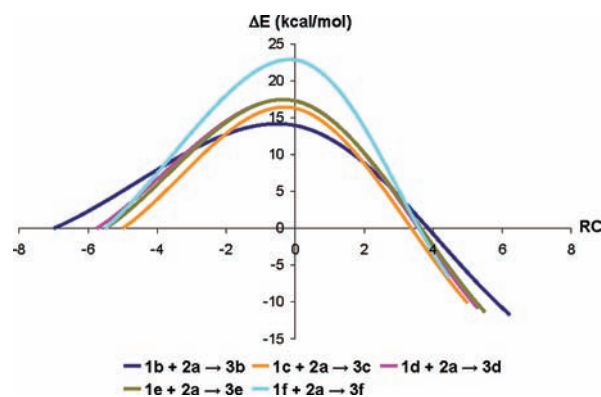


Figure 3. Plot of the IRC (in bohr/amu^{1/2}) versus energy (kcal/mol, relative to diene + **2a**) starting from the **TS1b**, **TS1c**, **TS1d**, **TS1e**, and **TS1f** computed at the B3LYP/6-311+G(2d,2p) level of theory.

HF/6-311+G(2d,2p) level of theory. In the context of the frontier molecular orbital (FMO) theory,¹⁶ a small preference for the NEDDA reaction will be for the neutral species **1a** with **2a** ($\delta\Delta E = \Delta E_{\text{IEDDA}} - \Delta E_{\text{NEDDA}} = 0.14 \text{ eV}$).¹⁷ The cycloadditions of the cationic species **1b–f** with **2a** are IEDDA reactions, and the preference increases by introducing Lewis acid **1f** ($\delta\Delta E_{\text{1f}} = -1.94 \text{ eV}$), alkyl groups **1b–e** ($\delta\Delta E_{\text{1e}} = -6.63 \text{ eV}$, $\delta\Delta E_{\text{1d}} = -9.55 \text{ eV}$, $\delta\Delta E_{\text{1c}} = -9.84 \text{ eV}$), and Brønsted acid **1b** ($\delta\Delta E_{\text{1b}} = -10.52 \text{ eV}$), while a large preference for the NEDDA reaction will be for the anionic species **1g** with **2a** ($\delta\Delta E_{\text{1g}} = 9.72 \text{ eV}$).

Table 1. HOMO and LUMO Eigenvalues (in eV) of **1a**, **2a**, and **1b–g** Calculated at the HF/6-311+G(2d,2p) Level of Theory

fragment	E_{HOMO}	E_{LUMO}	$\Delta E_{\text{IEDDA}}^a$	$\Delta E_{\text{NEDDA}}^b$	$\delta\Delta E^c$
1a	-9.67	1.74	12.09	11.95	0.14
1b	-16.01	-2.58	7.77	18.29	-10.52
1c	-15.60	-2.31	8.04	17.88	-9.84
1d	-15.45	-2.18	8.17	17.73	-9.55
1e	-12.65	-2.05	8.30	14.93	-6.63
1f	-11.22	1.21	11.56	13.50	-1.94
1g	-3.36	5.01	15.36	5.64	9.72
2a	-10.35	2.28			

$$^a \Delta E_{\text{NEDDA}} = E_{\text{LUMOdieneophile}} - E_{\text{HOMOdiene}} \quad ^b \Delta E_{\text{IEDDA}} = E_{\text{LUMOdiene}} - E_{\text{HOMOdieneophile}} \quad ^c \delta\Delta E = \Delta E_{\text{IEDDA}} - \Delta E_{\text{NEDDA}}$$

There is a direct correlation between the $\delta\Delta E$ and the activation energy E_a values calculated at the same level of theory HF/6-311+G(2d,2p) (see Tables S1 and S3 in the Supporting Information): $E_a = 1.00 \delta\Delta E + 44.78$

(16) (a) Fukui, K.; Yonezawa, T.; Shingu, H. *J. Chem. Phys.* **1952**, *20*, 722. (b) Fukui, K.; Yonezawa, T.; Nagata, C.; Shingu, H. *J. Chem. Phys.* **1954**, *22*, 1433.

(17) The NEDDA or IEDDA reaction preference is obtained by $\delta\Delta E = \Delta E_{\text{IEDDA}} - \Delta E_{\text{NEDDA}}$, where $\Delta E_{\text{NEDDA}} = E_{\text{LUMOdieneophile}} - E_{\text{HOMOdiene}}$ and $\Delta E_{\text{IEDDA}} = E_{\text{LUMOdiene}} - E_{\text{HOMOdieneophile}}$. Positive (negative) $\delta\Delta E$ values indicate preference for the NEDDA (IEDDA) reaction.

($R^2 = 0.95$). Additionally, Figure 4 shows an inverse correlation between the $\Delta\delta E$ values with the number of protons N_p for the cationic **1b** ($N_p = 1$), neutral **1a** ($N_p = 0$), and anionic **1g** ($N_p = -1$) species; $\Delta\delta E = -10.12N_p - 0.22$ ($R^2 = 0.99$). Thus, the FMO analysis for the cycloaddition reactions between **1a**, **1b–f**, and **1g** with **2a** is in agreement in predicting the cycloaddition reactions of **1b–f**, easier than **1a** and much easier than **1g** with **2a**.

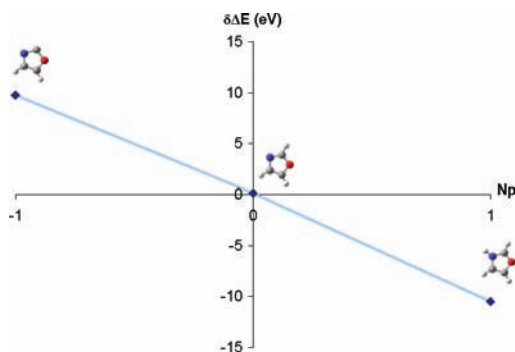


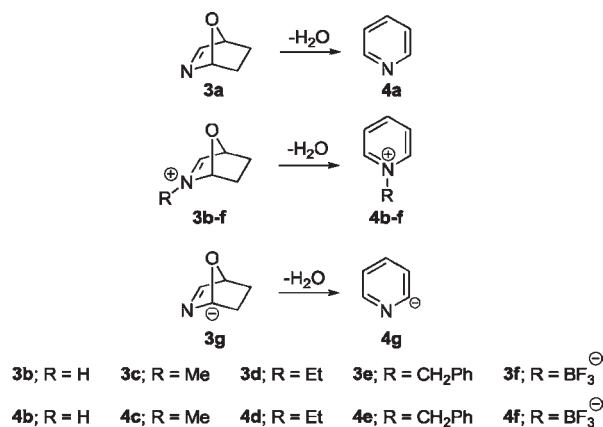
Figure 4. Fit line relating the $\Delta\delta E$ values with the number of protons N_p for the cationic **1b** ($N_p = 1$), neutral **1a** ($N_p = 0$), and anionic **1g** ($N_p = -1$) species.

Molecular orbital calculations (SCF-MO and KS-MO)¹⁸ were performed to study the aromatization reactions of the Diels–Alder cycloadducts **3a**, **3b–3f**, and **3g** to obtain pyridine **4a** and its pyridinium ions **4b–f** and **4g** (see Scheme 3). In general, the results obtained with the SCF-MO and KS-MO calculations followed the same trend.¹¹ Tables S5 and S6 in Supporting Information show that all of the unimolecular reactions are quite exothermic, with a heat of reaction of the Diels–Alder cycloadducts **3b**, **3c**, **3d**, **3e**, and **3f** by about 5–10 kcal/mol lower than the reactions of **3a** and **3g**. Not only are the reactions exothermic, they are also spontaneous with favorable entropy, by about $T\Delta S^\circ = 13$ kcal/mol. Therefore, the preference for the aromatization follows the trend **3b** > **3c** > **3d** > **3e** > **3f** > **3a** > **3g**.

From these data, we conclude that the electron-rich diene oxazolium anion will decelerate the NEDDA reaction rate, increasing the activation barrier, and the process becomes substantially endothermic. In contrast, the ability of the electron-deficient diene oxazolium cation to participate in the IEDDA reaction to obtain the Diels–Alder cycloadduct stems from the low activation barrier and the reaction exothermicity. The IEDDA reaction preference increases by attaching an alkyl group, or Lewis, or Brønsted acids to the oxazole nitrogen atom. Additionally, the high exothermicity of the dehydration reaction of the cationic Diels–Alder cycloadducts favors the formation of

the pyridinium cations. Therefore, the proton-assisted process is the key to realizing the potential azadiene oxazole ring Diels–Alder strategy.¹⁹ Experimental proof of the proposed mechanism was provided 40 years ago by the condensation of 5-ethoxy-4-methyloxazolium-protonated cation with the anion of β -acetylacrylic acid, and the substituted pyridinium cation was isolated from the reaction mixture at room temperature.^{4a} The cycloaddition reaction of neutral 5-fluoro-2,4-bis(trifluoromethyl)oxazole with ethylene does not occur under mild conditions; the reaction mixture needs to be heated in a steel autoclave at 110 °C for 10 h.^{4b} More drastic conditions are required for the reactions with more electrophilic dienophiles to proceed. Such dienophiles as tetracyanoethylene or maleic anhydride are not involved in cycloaddition reactions even at 180–200 °C. Our studies of the experimental reactivity of the systems are underway and will be reported in due course.

Scheme 3



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Supporting Information Available. Complete ref 9, Cartesian coordinates, electronic and zero-point energies, and thermochemical data for fully optimized geometries of **1a–g**, **2a**, **3a–g**, **4a–g**, and **TS1a**, **TS1b–f**, and **TS1g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(18) Calculations at the HF/6-31+G(d,p), HF/6-311+G(2d,2p), MP2/6-31+G(d,p), MP2/6-311+G(2d,2p), B3LYP/6-31+G(d,p), B3LYP/6-311+G(2d,2p), BHandHLYP/6-31+G(d,p), and BHandHLYP/6-311+G(2d,2p) levels were carried out.

(19) The global reaction **1b** + **2a** \rightarrow **4b** is exothermic and spontaneous and suffers from a very small penalty of entropy of $T\Delta S = 1.5$ kcal/mol.