Natural orbital Fukui function and application in understanding cycloaddition reaction mechanisms

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S1. Fukui Function

Within a spin-polarized density-functional theory (SP-DFT) conceptual framework,[1-4] the electron density $\rho(\mathrm{r})$ can be defined in terms of the α-spin and β-spin orbital populations:[5]

$$\rho(\mathrm{r}) = \rho_\alpha(\mathrm{r}) + \rho_\beta(\mathrm{r}) \tag{1}$$

In the Kohn-Sham (KS) approach, $\rho_\alpha(\mathrm{r})$ and $\rho_\beta(\mathrm{r})$ follow the normalization,

$$n_\alpha = \int \rho_\alpha(\mathrm{r})d\mathrm{r}\,,\ n_\beta = \int \rho_\beta(\mathrm{r})d\mathrm{r} \tag{2}$$

while the total electron number N is

$$N = N_\alpha + N_\beta \tag{3}$$

Therefore, the corresponding Fukui functions for the α-spin and β-spin cases are represented as follows[5]

$$f_{\alpha\alpha}(\mathrm{r}) = \left(\frac{\partial \rho_\alpha(\mathrm{r})}{\partial N_\alpha}\right)_{n_\beta, v(\mathrm{r})} \tag{4}$$

$$f_{\beta\alpha}(\mathrm{r}) = \left(\frac{\partial \rho_\beta(\mathrm{r})}{\partial N_\alpha}\right)_{n_\beta, v(\mathrm{r})} \tag{5}$$

$$f_{\alpha\beta}(\mathrm{r}) = \left(\frac{\partial \rho_\alpha(\mathrm{r})}{\partial N_\beta}\right)_{n_\alpha, v(\mathrm{r})} \tag{6}$$

$$f_{\beta\beta}(\mathrm{r}) = \left(\frac{\partial \rho_\beta(\mathrm{r})}{\partial N_\beta}\right)_{n_\alpha, v(\mathrm{r})} \tag{7}$$

where $\int f_{\alpha\alpha}(\mathrm{r})d\mathrm{r} = \int f_{\beta\beta}(\mathrm{r})d\mathrm{r} = 1$ and $\int f_{\beta\alpha}(\mathrm{r})d\mathrm{r} = \int f_{\alpha\beta}(\mathrm{r})d\mathrm{r} = 0$.

Using the finite difference approximation, in the case when an electron is added to the α-spin electrons set, that is, $\Delta N_\alpha = 1$ and $\Delta N_\beta = 0$, so

$$f^+_{\alpha\alpha}(\mathrm{r}) = \left(\frac{\partial \rho_\alpha(\mathrm{r})}{\partial N_\alpha}\right)^+_{n_\beta, v(\mathrm{r})} \cong \frac{\rho^+_\alpha(\mathrm{r}) - \rho^0_\alpha(\mathrm{r})}{N^0_\alpha + 1 - N^0_\alpha} = \rho^+_\alpha(\mathrm{r}) - \rho^0_\alpha(\mathrm{r}) \tag{8}$$

$$f_{\beta\alpha}^{+}(\mathrm{r}) = \left(\frac{\partial \rho_\beta(\mathrm{r})}{\partial N_\alpha}\right)_{n_\beta, v(\mathrm{r})}^{+} \cong \frac{\rho_\beta^{+}(\mathrm{r}) - \rho_\beta^{0}(\mathrm{r})}{N_\alpha^0 + 1 - N_\alpha^0} = \rho_\beta^{+}(\mathrm{r}) - \rho_\beta^{0}(\mathrm{r}) \tag{9}$$

when an electron is removed from the *β*-spin electrons set, that is, $\Delta N_\alpha = 0$ and $\Delta N_\beta = -1$, so

$$f_{\alpha\beta}^{-}(\mathrm{r}) = \left(\frac{\partial \rho_\alpha(\mathrm{r})}{\partial N_\beta}\right)_{n_\alpha, v(\mathrm{r})}^{-} \cong \frac{\rho_\alpha^{-}(\mathrm{r}) - \rho_\alpha^{0}(\mathrm{r})}{N_\beta^0 - 1 - N_\beta^0} = \rho_\alpha^{0}(\mathrm{r}) - \rho_\alpha^{-}(\mathrm{r}) \tag{10}$$

$$f_{\beta\beta}^{-}(\mathrm{r}) = \left(\frac{\partial \rho_\beta(\mathrm{r})}{\partial N_\beta}\right)_{n_\alpha, v(\mathrm{r})}^{-} \cong \frac{\rho_\beta^{+}(\mathrm{r}) - \rho_\beta^{0}(\mathrm{r})}{N_\beta^0 - 1 - N_\beta^0} = \rho_\beta^{0}(\mathrm{r}) - \rho_\beta^{-}(\mathrm{r}) \tag{11}$$

For the natural bond orbital occupancy, n_{nbo}, due to the spin multiplicity change, it is divided into the *α*-spin and *β*-spin orbital contributions:

$$n_{\mathrm{nbo}} = n_{\alpha,\mathrm{nbo}} + n_{\beta,\mathrm{nbo}} \tag{12}$$

Then the total natural bond orbital occupancies are represented as

$$N = \sum_{\mathrm{nbo}} n_{\mathrm{nbo}} = \sum_{\alpha,\mathrm{nbo}} n_{\alpha,\mathrm{nbo}} + \sum_{\beta,\mathrm{nbo}} n_{\beta,\mathrm{nbo}} \tag{13}$$

where $N_{\alpha,\mathrm{nbo}} = \sum_{\alpha,\mathrm{nbo}} n_{\alpha,\mathrm{nbo}}$, $N_{\beta,\mathrm{nbo}} = \sum_{\beta,\mathrm{nbo}} n_{\beta,\mathrm{nbo}}$, and in the neutral molecule, $N_{\alpha,\mathrm{nbo}}^0 = N_{\beta,\mathrm{nbo}}^0$, $n_{\alpha,\mathrm{nbo}}^0 = n_{\beta,\mathrm{nbo}}^0$.

Then the condensed Fukui functions (in the paper)

$$f_{\mathrm{nbo}}^{+} = \left(\frac{\partial n_{\mathrm{nbo}}}{\partial N}\right)_{v(\mathrm{r})}^{+} = n_{\mathrm{nbo}}^{N+1} - n_{\mathrm{nbo}}^{N} \tag{14}$$

$$f_{\mathrm{nbo}}^{-} = \left(\frac{\partial n_{\mathrm{nbo}}}{\partial N}\right)_{v(\mathrm{r})}^{-} = n_{\mathrm{nbo}}^{N} - n_{\mathrm{nbo}}^{N-1} \tag{15}$$

can be extended to the case when $\Delta N_{\alpha,\mathrm{nbo}} = 1$ and $\Delta N_{\beta,\mathrm{nbo}} = 0$, which are approximated by

$$f_{\alpha\alpha,\mathrm{nbo}}^{+} = \left(\frac{\partial n_{\alpha,\mathrm{nbo}}}{\partial N_{\alpha,\mathrm{nbo}}}\right)_{v(\mathrm{r})}^{+} = n_{\alpha\alpha,\mathrm{nbo}}^{N+1} - n_{\alpha\alpha,\mathrm{nbo}}^{N} \tag{16}$$

$$f^{+}_{\beta\alpha,\mathrm{nbo}} = \left(\frac{\partial n_{\beta,\mathrm{nbo}}}{\partial N_{\alpha,\mathrm{nbo}}}\right)^{+}_{v(\mathrm{r})} = n^{N+1}_{\beta\alpha,\mathrm{nbo}} - n^{N}_{\beta\alpha,\mathrm{nbo}} \tag{17}$$

where $f^{+}_{\mathrm{nbo}} = f^{+}_{\alpha\alpha,\mathrm{nbo}} + f^{+}_{\beta\alpha,\mathrm{nbo}}$.

Similarly, in the case $\Delta N_{\alpha,\mathrm{nbo}} = 0$ and $\Delta N_{\beta,\mathrm{nbo}} = -1$, the Fukui function of Eq. (13) can be represented as

$$f^{-}_{\alpha\beta,\mathrm{nbo}} = \left(\frac{\partial n_{\alpha,\mathrm{nbo}}}{\partial N_{\beta,\mathrm{nbo}}}\right)^{-}_{v(\mathrm{r})} = n^{N}_{\alpha\beta,\mathrm{nbo}} - n^{N-1}_{\alpha\beta,\mathrm{nbo}} \tag{18}$$

$$f^{-}_{\beta\beta,\mathrm{nbo}} = \left(\frac{\partial n_{\beta,\mathrm{nbo}}}{\partial N_{\beta,\mathrm{nbo}}}\right)^{-}_{v(\mathrm{r})} = n^{N}_{\beta\beta,\mathrm{nbo}} - n^{N-1}_{\beta\beta,\mathrm{nbo}} \tag{19}$$

where $f^{-}_{\mathrm{nbo}} = f^{-}_{\alpha\beta,\mathrm{nbo}} + f^{-}_{\beta\beta,\mathrm{nbo}}$.

S2. NBO analysis and NOFFs

Data Processing

Due to the spin multiplicity change (caused by electron addition to, or depletion from, a molecular system), some NBOs would appear or disappear relative to those in the neutral one when an electron addition to, or depletion from a molecule. For the NBO, if it is not present in the neutral molecule but in the anion (an electron is added) or cation (an electron is removed), its orbital occupancy is considered to be "zero" in the neutral molecule. Analogously, with regard to the NBO that presents in the neutral molecule but disappears in the anion or cation, its orbital occupancy is "zero" in such case.

Data Analysis

It is shown that a molecule possesses many natural orbitals for its neutral, anion and cation systems, but not all the orbitals play the decisive roles in the chemical reaction. For example, it is well-known that the two C=C double bonds in 1,3-butadiene and one C=C double bond in ethylene directly take part in the cycloaddition reaction, they reorganize each other to give a six-membered ring containing one C=C double bond and two new sigma bonds. In this process, the two C=C double bonds in 1,3-butadiene and one C=C double bond in ethylene form two new sigma bonds, while the C–C single bond in 1,3-butadiene reorganizes to be a C=C double bond. Therefore, their properties would substantially determine the reaction process, though the other bonds (*e.g.*, C–H bond) would affect the properties of these double bonds. Because the C–H bond may also change but they are not directly involved in the bond making or breaking, and remains as C–H bond in the product. As a result, the reactivities of the double bonds based on NOFFs will be used to interpret the mechanism of [1,3-butadiene+ethylene] cycloaddition as well as other cycloaddition reactions.

S3. Other cycloaddition reactions

[4+2] cycloaddition reaction

Another [4+2] cycloaddition reaction examined by the NOFF is heterodiene reacting with methyl vinyl ketone (Scheme S1).[6] NOFF values of the C1=N2 and C3=S4 double bonds in heterodiene and those of the C1=C2 double bond in methyl vinyl ketone are listed in Table S1. The amphiphilic BD(2)C1–N2 and electron-donating BD(2)C3–S4 bonding orbitals of heterodiene are observed; the BD(1)C1–N2 is inactive while the BD(1)C3–S4 is able to accept electrons. The BD*(1)C1–N2, BD*(1)C3–S4 and BD*(2)C3–S4 seem to be able to donate electrons though it is impossible, and only BD*(2)C1–N2 is capable of accepting electrons. For methyl vinyl ketone, its BD(1)C1–C2 is inactive and the BD(2)C1–C2 is capable of donating electrons; the BD*(1)C1–C2 is amphiphilic, and the BD*(2)C1–C2 seems to be electron-donating. The process of cycloaddition reaction may hence start with the BD(2)C3–S4 of the C3=S4 in heterodyne donating electrons to an antibonding orbital of the C1=C2 (*e.g.*, BD*(1)C1–C2) in methyl vinyl ketone, followed by the BD(2)C1–C2 of the C1=C2 in methyl vinyl ketone donating electrons to the BD*(2)C1–N2 of the C1=N2 in heterodyne, resulting in the six-membered ring (Fig. S1). Once again, from the perspective of whether a bond is inclined to donate or accept electrons, NOFF can shed light on the reaction mechanism.

[2+2] cycloaddition of ketenes

NOFFs were used to understand the well-known [2+2] cycloaddition reactions of ketenes. Ketenes have been shown to be reactive with both electrophiles and nucleophiles.[7] The [2+2] cycloaddition reaction studied (Scheme S2) includes four ketenes (Y=H, NH_2, Cl, or CN) and three isoelectronic ketenophiles (ethylene, methylenimine, and formaldehyde).[8]

Frontier-orbital analyses suggest that the ketene [2+2] cycloaddition is initiated by the interaction between the π orbital and/or the lone pair orbital of a ketenophile and the LUMO of a ketene; this dominant charge transfer step (CT1) drives the formation of the first covalent bond. The second dominant charge transfer step (ct2), from the HOMO of the ketene to the π^* orbital of the ketenophile, drives the formation of the second covalent bond.[8] The π orbital and the lone pair orbital of a ketenophile donate electrons and act as nucleophiles; the LUMO of a ketene accepts electrons and is electrophilic. Similarly, the HOMO of the ketene is nucleophilic and the

π^* orbital of the ketenophile is electrophilic. It is traditional to study ambiphilic reagents like ketenes and ketenophiles using the derivative of the Fukui function, called the dual descriptor.[9-14] However, because the electron-donating or accepting capability of orbitals, is readily derived from the NOFF values, it should also be possible to analyze the reaction mechanism of the [2+2] cycloadition using NOFF. We will show that the NOFF approach has the advantage of providing a more detailed, orbital-level, description; in this way NOFF bridges the gap between molecular orbital theory and conceptual DFT.

Table S2 represents the NOFFs of the C=C double bonds in the four ketenes and the C=X double bonds in the two isoelectronic ketenophiles, and those for the C=C double bond in ethylene can be seen in Table 2 (in the paper). All of the BD(2)C1–C2 bonding orbitals in the four ketenes are able to donate electrons, as evidenced by the positive value of the electrophilic Fukui function f_{nbo}^{-}, while their BD*(1)C1–C2 antibonding orbitals are able to accept electrons. Their BD(1)C1–C2 are inactive because of the negative f_{nbo}^{+} and f_{nbo}^{-}. It is noted that some of their BD(2)C1–C2 bonding orbitals, and BD*(1)C1–C2 and BD*(2)C1–C2 antibonding orbitals have the amphiphilic characters, and some BD*(2)C1–C2 antibonding orbitals seem to be able to donate electrons. For ethylene, both of its BD(1)C1–C4 and BD*(2)C1–C4 orbitals are able to accept electrons, while its BD(2)C1–C4 and BD*(1)C1–C4 orbitals are able to donate electrons. For H_2C=NH, the BD(2)C1–N2 and BD*(1)C1–N2 orbitals are inactive, but its BD(1)C1–N2 and BD*(2)C1–N2 orbitals only have the abilities of accept electrons. With regard to H_2C=O, its BD(1)C1–O2 is able to donate electrons, whereas its BD(2)C1–O2 and BD*(1)C1–O2 orbitals are inactive, and its BD*(2)C1–O2 orbital is capable of accepting electrons.

Consequently, the reaction mechanism of the [2+2] cycloaddition can be determined by the electron accepting character of an antibonding orbital and the electron donating character of a bonding orbital (Fig. S2, with the exception of H_2C=NH). At the onset of the reaction, one of the bonding orbitals of reactant **R1** donates electrons to one of the antibonding orbitals of reactant **R2**, and, at the same time, one of **R1**’s antibonding orbitals obtains electrons from one of **R2**’s bonding orbitals. The charge transfer processes form a circular loop with two covalent bonds constructed, resulting in the formation of a four-membered ring. The mechanism proves the key role of charge transfer in the cycloaddition reactions,[8] and the NOFF is able to predict the electronic philicity of the associated bonds and thereby the charge transfer direction.

1,3-Dipolar cycloaddition

1,3-dipolar cycloadditions[15,16] have been studied by frontier molecular orbital (FMO) theory to interpret the reactivity and regioselectivity based on the electronic properties of reactants.[17-22] CDFT has also been used to explore the reactions.[23] A recent report by Ess and Houk shows that the distortion energy from 1,3-dipole or dipolarophile to the transition state determines the reactivity differences among 1,3-dipoles.[24,25] However, finding the transition state and associated energy level in a chemical reaction can be difficult. Herein, a representative 1,3-dipolar cycloaddition between fulminic acid and acetylene[26] (Scheme S3) was studied by NOFF. Shown in Table S3, only the BD(3)N2–C3 bonding orbital of the N2≡C3 bond of fulminic acid is capable of donating electrons, while its BD^*(1)N2–C3 is amphiphilic, and its BD^*(2)N2–C3 and BD^*(3)N2–C3 seem to be able to donating electrons. For the O1=N2 bond, only the amphiphilic character of its BD^*(1)O1–N2 is seen. Acetylene has three bonding orbitals and three antibonding orbitals of its C≡C triple bond. It shows that the BD(1)C1–C2, BD(2)C1–C2 and BD(3)C1–C2 can donate electrons, but the BD*(1)C1–C2 and BD*(2)C1–C2 are inactive, and the BD*(3)C1–C2 represents the amphiphilic character. Hence, the 1,3-dipolar cycloaddition of fulminic acid to acetylene initiates the circular loop by forming covalent bonds between C2 and O1 and between C1 and C3 , resulting in a five-membered heterocycle (Fig. S3). The NOFFs clearly point out the reactivity site in 1,3-dipolar cycloaddition and the corresponding charge transfer direction, that is, C3 of fulminic acid acts as bond donor center while O1 acts as the bond acceptor center. It is consistent with the previous study[26] that C3 is more likely to be the bond donor center in terms of local softness (a CDFT concept[27, 28]).

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Table S1 NOFFs (unit in electrons) of the C1=N2 and C3=S4 double bonds in heterodiene and of the C1=C2 double bond in methyl vinyl ketone, and the corresponding reactivities derived from the NOFF values.[a]

	Natural orbital	f^{+}_{nbo}	f^{-}_{nbo}	Reactivity
Heterodiene	BD(1)C1–N2	–0.00100	–0.00042	Inactive
	BD(2)C1–N2	0.07466	0.08689	Amphiphilic
	BD(1)C3–S4	0.00134	–0.00316	Nucleophilic
	BD(2)C3–S4	–0.97372	1.94100	Electrophilic
	BD*(1)C1–N2	–0.00097	0.00060	Electrophilic
	BD*(2)C1–N2	0.03303	–0.05336	Nucleophilic
	BD*(1)C3–S4	–0.00722	0.00197	Electrophilic
	BD*(2)C3–S4	–0.21159	0.34788	Electrophilic
Methyl vinyl ketone	BD(1)C1–C2	–0.00131	–0.00023	Inactive
	BD(2)C1–C2	–0.96315	0.97478	Electrophilic
	BD*(1)C1–C2	0.00093	0.00333	Amphiphilic
	BD*(2)C1–C2	–0.01184	0.01474	Electrophilic

[a] BD denotes bonding orbital; BD* denotes antibonding orbital. For BD and BD*, (1) denotes σ orbital, (2) denotes π orbital.

Table S2 NOFFs (unit in electrons) of the C=C double bonds in the four ketenes (Y–HC=C=O, Y=H, NH_2, Cl, and CN) and the C=X double bonds in the two isoelectronic ketenophiles (methylenimine and formaldehyde), and corresponding reactivities derived from the NOFF values.[a]

	Natural orbital	f^{+}_{nbo}	f^{-}_{nbo}	Reactivity
$H_2C=C=O$	BD(1)C1–C2	–0.00023	–0.00182	Inactive
	BD(2)C1–C2	0.00146	0.99511	Amphiphilic
	BD^*(1)C1–C2	0.00035	0.00273	Amphiphilic
	BD^*(2)C1–C2	–0.00748	0.13861	Electrophilic
$H_2NHC=C=O$	BD(1)C1–C2	–0.00203	–0.00269	Inactive
	BD(2)C1–C2	–0.00174	0.98128	Electrophilic
	BD^*(1)C1–C2	0.00097	–0.00163	Nucleophilic
	BD^*(2)C1–C2	–0.00754	0.14401	Electrophilic
ClHC=C=O	BD(1)C1–C2	–0.00173	–0.00187	Inactive
	BD(2)C1–C2	–0.22277	0.99218	Electrophilic
	BD^*(1)C1–C2	0.00072	–0.00027	Nucleophilic
	BD^*(2)C1–C2	0.01911	0.15594	Amphiphilic
NCHC=C=O	BD(1)C1–C2	–0.00438	–0.00227	Inactive
	BD(2)C1–C2	–0.03918	0.94312	Electrophilic
	BD^*(1)C1–C2	0.00044	0.00210	Amphiphilic
	BD^*(2)C1–C2	0.01239	0.16122	Amphiphilic
$H_2C=NH$	BD(1)C1–N2	0.00027	–0.00036	Nucleophilic
	BD(2)C1–N2	–0.00173	–0.00049	Inactive
	BD^*(1)C1–N2	–0.00029	–0.00034	Inactive
	BD^*(2)C1–N2	0.00040	0.00000	Nucleophilic
$H_2C=O$	BD(1)C1–O2	–0.00009	0.00029	Electrophilic
	BD(2)C1–O2	–0.00116	–0.00020	Inactive
	BD^*(1)C1–O2	–0.00002	–0.00027	Inactive
	BD^*(2)C1–O2	0.00004	0.00000	Nucleophilic

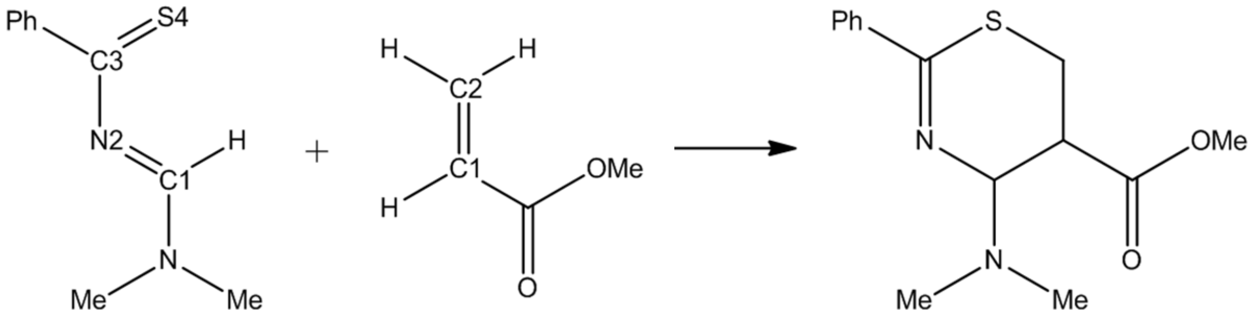
[a] BD denotes bonding orbital; BD* denotes antibonding orbital. For BD and BD*, (1) denotes σ orbital, (2) denotes π orbital.

Table S3 NOFFs (unit in electrons) of the O1=N2 double bond and N2≡C3 triple bond in fulminic acid and the C≡C triple bond in acetylene, and corresponding reactivities derived from the NOFF values.[a]

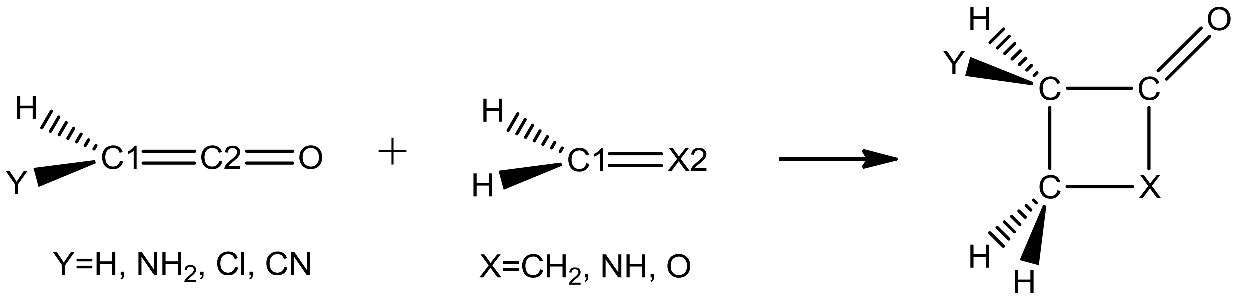
	Natural orbital	f^{+}_{nbo}	f^{-}_{nbo}	Reactivity
HC≡N=O	BD(1)O1–N2	–0.00223	–0.00071	Inactive
	BD(2)O1–N2	0.00000	–0.88708	Inactive
	BD(1)N2–C3	–0.00336	–0.00248	Inactive
	BD(2)N2–C3	–0.00113	–0.00125	Inactive
	BD(3)N2–C3	–0.01171	0.99658	Electrophilic
	BD^{*}(1)O1–N2	0.00038	0.00100	Amphiphilic
	BD^{*}(1)N2–C3	0.00204	0.00594	Amphiphilic
	BD^{*}(2)N2–C3	–0.02096	0.07689	Electrophilic
	BD^{*}(3)N2–C3	–0.06596	0.17976	Electrophilic
HC≡CH	BD(1)C1–C2	–0.00018	0.00005	Electrophilic
	BD(2)C1–C2	–0.00018	0.00047	Electrophilic
	BD(3)C1–C2	–0.00262	0.99390	Electrophilic
	BD^{*}(1)C1–C2	0.00000	0.00000	Inactive
	BD^{*}(2)C1–C2	0.00000	–0.00060	Inactive
	BD^{*}(3)C1–C2	0.00928	0.00760	Amphiphilic

[a] BD denotes bonding orbital; BD* denotes antibonding orbital. For BD and BD*, (1) denotes σ orbital, (2) denotes the first π orbital, (3) denotes the second π orbital.

Scheme S1 [4+2] cycloaddition reaction of heterodiene to methyl vinyl ketone.



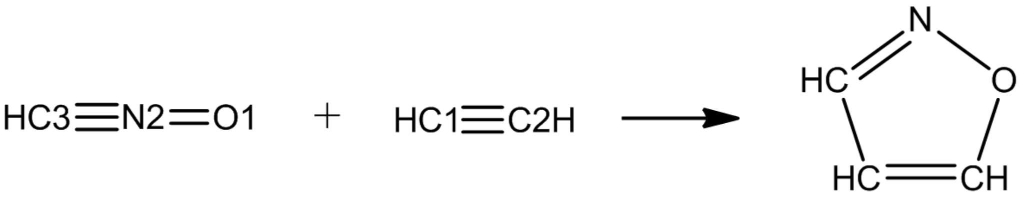
Scheme S2 [2+2] cycloaddition reaction.



Y=H, NH_2, Cl, CN

X=CH_2, NH, O

Scheme S3 1,3-dipolar cycloaddition reaction.



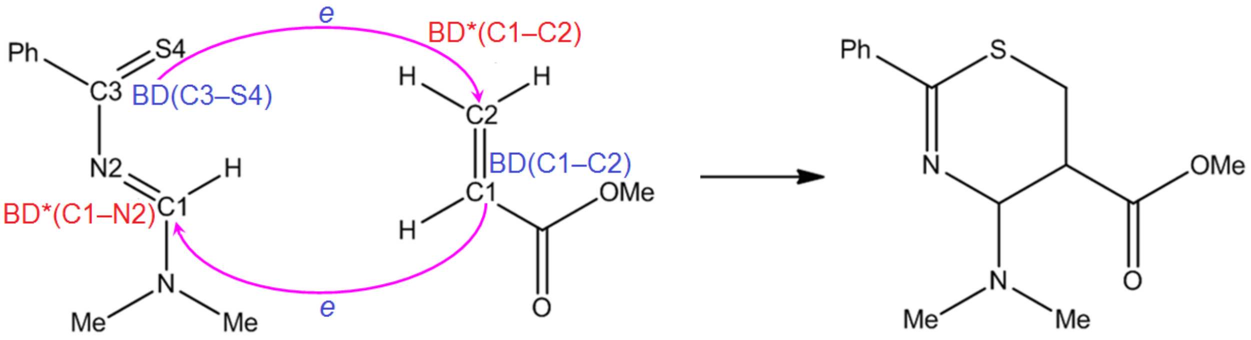


Fig. S1 Proposed mechanism of heterodiene and methyl vinyl ketone [4+2] cycloaddition reaction.

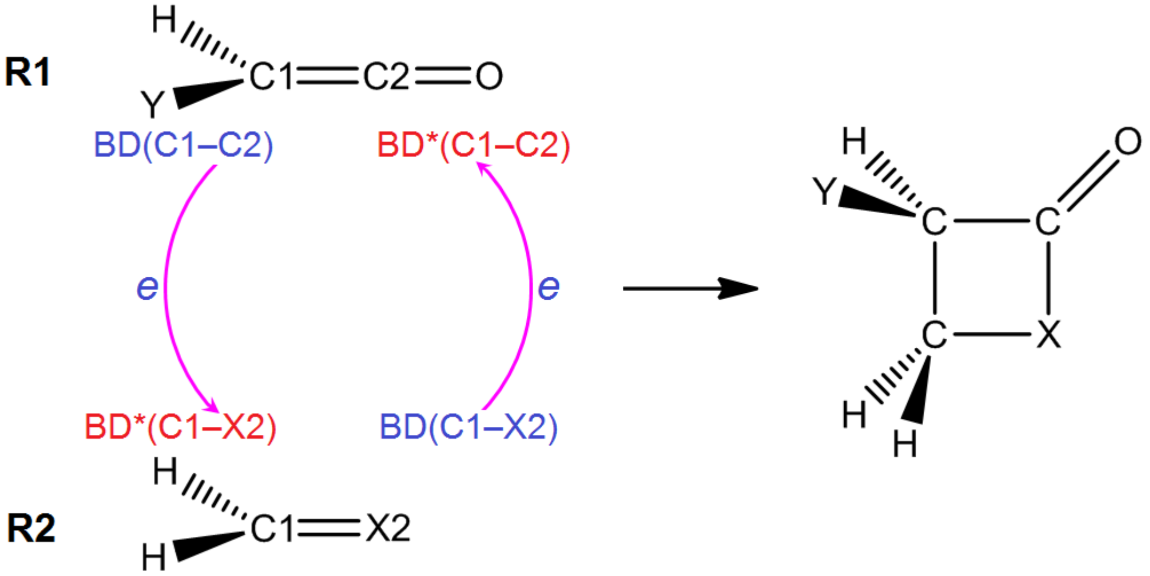


Fig. S2 Proposed mechanism of [2+2] cycloaddition reaction.

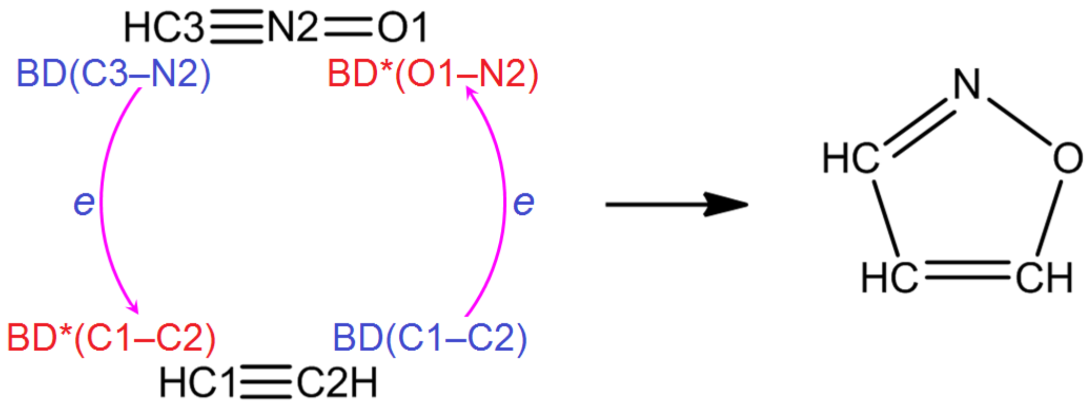


Fig. S3 Proposed mechanisms of 1,3-dipolar cycloaddition reaction.