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NHC-Catalyzed and Brønsted Acid Copromoted *E* → *Z* Isomerization Mode of Breslow Intermediates Leading to Ralfuranones

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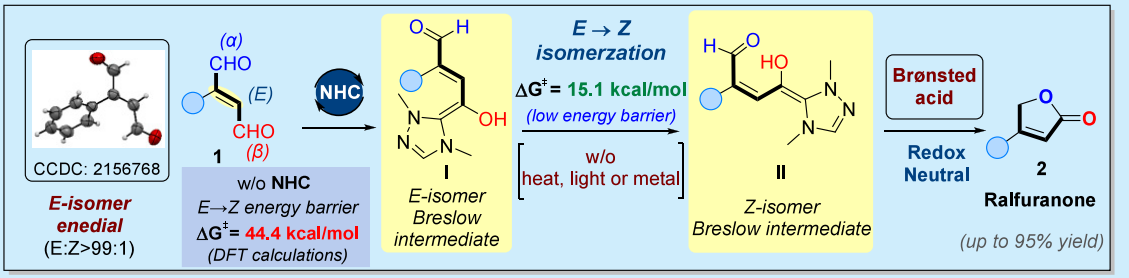

ABSTRACT: Different *Z*/*E*-isomers of functional molecules display distinct chemical and biological activities. The *E* → *Z* isomerization reaction is a contra-thermodynamic direction and presents a long-standing challenge in synthetic transformation. To date, organic catalysis methods for manipulating *E*/*Z* isomerization are still under development. Here we show a new N-heterocyclic carbene (NHC)-catalyzed *E*/*Z* isomerization mode. The *E*-isomer enedial undergoes *E*/*Z* isomerization to give a *Z*-isomer Breslow intermediate via NHC catalysis, and an intramolecular hydrogen bond can greatly stabilize this conformation. Subsequently, the Brønsted acid promotes the further redox-neutral reaction. The desired ralfuranone products obtained from our method can be readily transformed to various functional molecules.

The *E*/*Z* isomerization of alkenes has always been a challenge since the discovery of alkenes themselves (Figure 1a). For simple alkenes, *Z* → *E* isomerization is thermodynamically favored.[1−3] Notably, different Z/*E*-isomers of functional molecules exhibit distinct chemical reactivities and biological activities.[4,5] In contrast, the *E* → *Z* isomerization reaction is contra-thermodynamic direction, which presents long-standing challenges in synthetic transformation.[2,3,6−8] Through sustained innovation coupled with the importance of Z/*E*-isomer alkenes in functional molecules, multiple methodologies and catalytic activation modes are now widely used to facilitate contra-thermodynamic reactions. Currently, numerous efficient methods for *E*/*Z* isomerization are available, which include photo-,[5,9−23] enzyme-,[21,24,25] and transition metal-catalysis,[26−37] as well as various types of synergistic and relay catalysis.[18,19,21,25] Among organocatalysts, amino- and carbene catalysts have also been utilized; the organic catalyst-bound *E*-isomer intermediates were obtained, and then, photoinduced *E* → *Z* isomerization reactions were achieved via photosensitization.[18,19] Until now, single organic catalysis methods for *E*/*Z* isomerization are still under development.

Such furanone derivatives are fundamental structural motifs in both natural and synthetic bioactive molecules (Figure 1b).[38−42] The ralfuranones include natural products ralfuranones A, B, and L.[39−43] Moreover, xenofuranone B has been reported to exhibit cytotoxic activity.[38−40,42,43] Flupyradifurone, as a new type of insecticide, was developed and marketed by Bayer.[44−46] For another, rofecoxib,[47−50] a noteworthy example of a dual inhibitor targeting lipoxygenase and cyclooxygenase was also developed.

Here we report a new and concise strategy that does not rely on any transition metal or light but instead utilizes simple N-heterocyclic carbene (NHC)[51−57] catalysts at mild conditions to achieve the *E* → *Z* isomerization. This approach enables the synthesis of ralfuranone products with Z-type C═C double bonds (Figure 1c). *E*-Isomer enedial (**1a**) served as a starting substrate. NHC reacted with the *β*-aldehyde group in substrate **1a** to generate the corresponding *E*-isomer Breslow intermediate **I**. The rotational energy barrier of its C═C double bond in Breslow intermediate **I** is extremely lower than that of substrate **1a** (*E* → *Z* $\triangle G^{\ddagger}$ = 44.4 kcal/mol, w/o NHC). Meanwhile, the intramolecular hydrogen bonding stabilized the *Z*-isomer Breslow intermediate. After that, it underwent an *E* → *Z* isomerization reaction to promote the intramolecular cycloaddition. Then, a Brønsted acid was employed as both a

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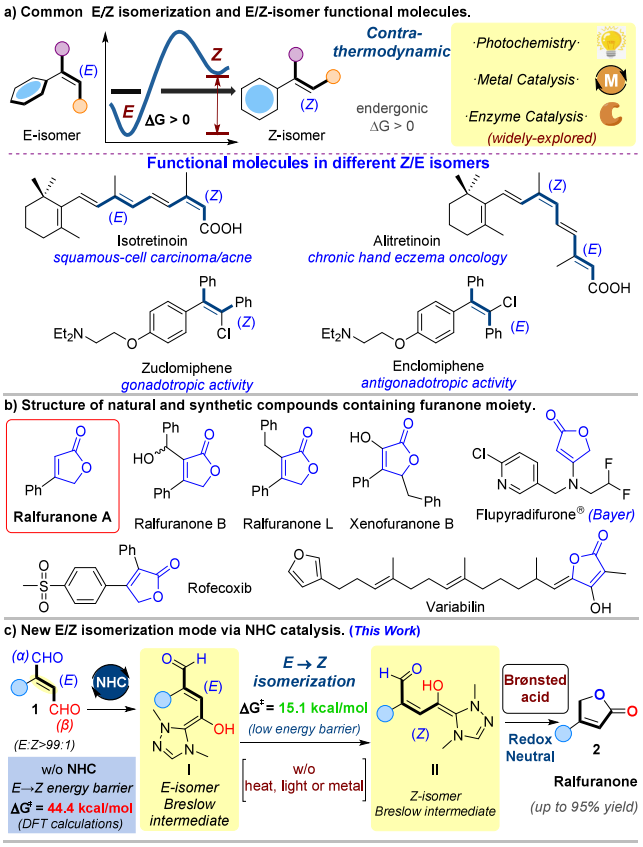


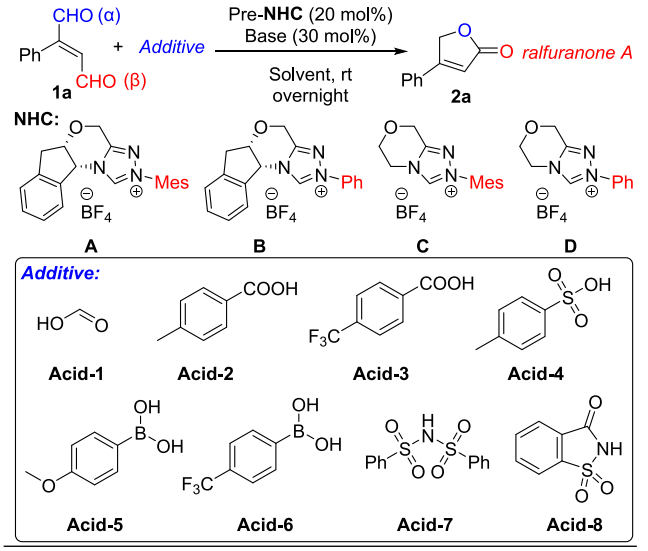
Figure 1. A. Representative *E*/*Z* isomerization reaction and *E*/*Z*-isomer functional molecules; B. Functional molecules containing a furanone moiety; C. Our proposed approach for the NHC-catalyzed *E*/*Z* isomerization mode.

proton source and oxidant. It can accelerate the process of a redox-neutral reaction and promote the shifting equilibria. The combination of NHC catalysts and Brønsted acids provides a good control in efficiently promoting the *E*/*Z* isomerization.

The initial study starts with the *E*-isomer enedial **1a** (Scheme 1). First, there was no product that could be obtained after 24 h without any additives (Scheme 1, Entry 1). After the reaction time was extended to 3 days, product **2a** (54% yield) could be clearly observed (Scheme 1, Entry 2). Then, a catalytic amount (20 mol %) of 4-(trifluoromethyl) benzoic acid (**Acid-3**) was explored, and the desired product **2a** can be obtained with 13% yield after 12 h (Scheme 1, Entry 3). Furthermore, various Brønsted acids were defined as the proton sources as well as oxidants (**Acid-1** to **8**). The desired product **2a** was disclosed in 83% isolated yield with THF as solvent and K_2CO_3 as base under aminoindanol-derived triazolium pre-NHC **A** (Scheme 1, Entry 6). Meanwhile, product **2a** also can be obtained with 59% yield when **Acid-8** was used (Scheme 1, Entry 11). This result was encouraging due to the high yield obtained under conventional conditions. After that, achiral NHC catalysts (**C** and **D**) were also investigated; the yield achieved was slightly higher when pre-NHC **C** was used (Scheme 1, Entry 13). Subsequently, the impact of bases and solvents was minimal (Scheme 1, Entries 15−20). Finally, the optimal reaction result was afforded, and product **2a** was provided in 89% isolated yield with solvent DCM (Scheme 1, Entry 20).

Once the optimal reaction condition had been determined, the substrate examples were explored (Scheme 2). Substituents

Scheme 1. Optimization of Reaction Conditions[a]



Entry	NHC	Additive	Base	Solvent	Yield [%][b]
1[c]	**A**	-	K_2CO_3	DCM	0
2[d]	**A**	-	K_2CO_3	DCM	54
3[e]	**A**	**Acid-3**	K_2CO_3	DCM	13
4	**A**	**Acid-1**	K_2CO_3	THF	0
5	**A**	**Acid-2**	K_2CO_3	THF	0
6	**A**	**Acid-3**	K_2CO_3	THF	83
7	**A**	**Acid-4**	K_2CO_3	THF	0
8	**A**	**Acid-5**	K_2CO_3	THF	0
9	**A**	**Acid-6**	K_2CO_3	THF	0
10	**A**	**Acid-7**	K_2CO_3	THF	0
11	**A**	**Acid-8**	K_2CO_3	THF	59
12	**B**	**Acid-3**	K_2CO_3	THF	80
13	**C**	**Acid-3**	K_2CO_3	THF	85
14	**D**	**Acid-3**	K_2CO_3	THF	76
15	**C**	**Acid-3**	Cs_2CO_3	THF	80
16	**C**	**Acid-3**	DABCO	THF	77
17	**C**	**Acid-3**	DBU	THF	85
18	**C**	**Acid-3**	K_2CO_3	EA	86
19	**C**	**Acid-3**	K_2CO_3	MeCN	83
20	**C**	**Acid-3**	K_2CO_3	DCM	89

[a]Unless otherwise specified, the reactions were conducted with **1a** (0.10 mmol), **Additives** (0.10 mmol), **NHCs** (0.02 mmol), bases (0.03 mmol), and solvents (2.0 mL) at room temperature for 12 h. [b]Isolated yield of **2a**. [c]No additive and reacted for 24 h. [d]No additive and reacted for over 3 days. [e]**Acid-3** (0.02 mmol).

possessing both electron-withdrawing and electron-donating groups could be installed on each (*para*-, *meta*-, or *ortho*-) position of the phenyl group in aldehydes, with the corresponding products afforded in good to excellent yields (**2a-2l**). Our approach could be prepared on larger scales with little impact on the yield of desired product **2a** (400.5 mg, 2.5 mmol, 80% yield, 19 h). The structure of **2a** was confirmed through X-ray diffraction analysis. Meanwhile, a slightly lower yield was observed when the 4-methylthio group appeared on

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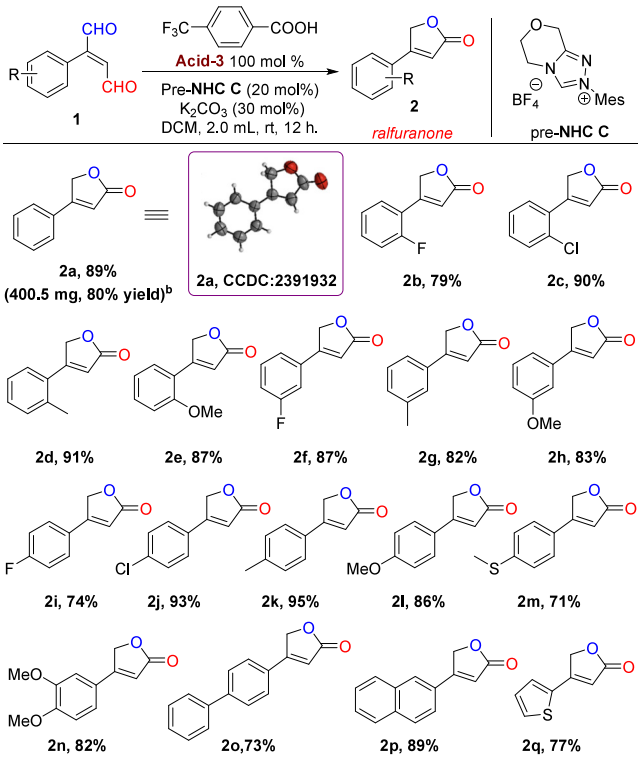
Scheme 2. Substrate Scope[a]

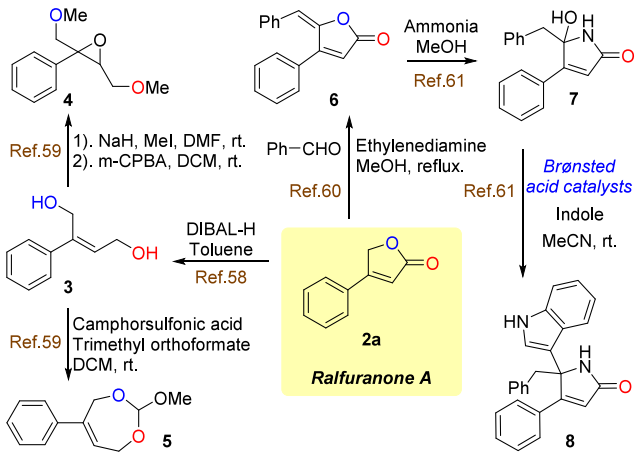


[a]Reaction conditions as stated in Scheme 1, Entry 20; yields were isolated yields after purification by column chromatography. [b]The reaction was carried out on a 2.5 mmol scale based on **1a**; reaction time: 19 h.

the *para*-position compared with the model reaction (**2m**). A multisubstituent reactant was also suitable for the construction of a reaction system like dimethoxy, and the corresponding product can afford excellent yield (**2n**). Replacement with biphenyl and naphthyl groups afforded good yields (**2o** and **2p**). A heterocyclic group, such as thiophene, was also used, and the corresponding product can be obtained with good yield (**2q**).

Ralfuranone A is an important functional molecule; the synthetic transformations have been reported widely (Scheme 3).[58−61] For example, White and co-workers reported that

Scheme 3. Synthetic Transformations



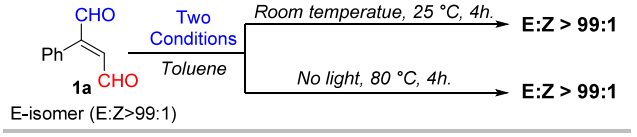
compound **3** can be synthesized by the reduction reaction of **2a** and DIBAL-H.[58] Then, compound **3** can be epoxidized with m-CPBA to form epoxide product **4** via the method reported by Kleij and co-workers in 2016.[59] Meanwhile, compound **3** can also react with trimethyl orthoformate to obtain product **5** under the catalysis of camphorsulfonic acid in the same literature.[59] Then, Song and co-workers reported that compound **6** can be obtained by reacting **2a** with benzaldehyde in the presence of ethylenediamine.[60] Subsequently, **6** can be reacted with a solution of NH_3 in MeOH to give γ-hydroxybutyrolactam **7**. After that, **7** can react with indole to synthesize compound **8** via Brønsted acid catalysis as Commeiras reported.[61]

In our previous work,[62] the structure of **1a** has been confirmed by X-ray diffraction (**CCDC**: 2156768). Combined with the ^{1}H NMR results (Supporting Information), it indicated that substrate **1a** is a single *E*-isomer enedial (*E*/*Z* > 99:1). It is worth noting that the desired ralfuranone products **2** contained a Z-type C=C double bond, while it was difficult for the C=C double bond in substrate **1a** to rotate directly and then continue the cyclization reaction. Therefore, it should undergo an *E* → *Z* isomerization process in the NHC-catalyzed reaction.

To investigate the process of *E* → *Z* isomerization in the reaction, some control experiments were employed (Scheme 4a). First, the geometric thermal stability of substrate **1a** was

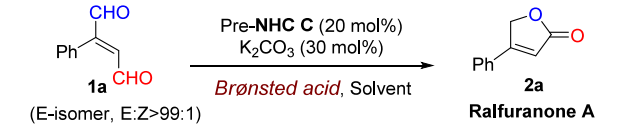
Scheme 4. Control Experiments of Mechanism Study

a) Thermodynamic stability studies.



E-isomer (E:Z>99:1)

b) Control experiments for mechanistic studies.



(E-isomer, E:Z>99:1) **Ralfuranone A**

1. w/o light, overnight.	86% yield
2. Temperature: 0°C, reaction time: 20 h.	85% yield
3. w/o NHC, reaction time: 3 days.	0% yield **1a** recovery rate: 93% **E:Z** = 99:1
4. w/o Brønsted acid, reaction time: 30 h.	41% yield E:Z of **1a** = 16:1

investigated. *E*-Isomer **1a** was dissolved in toluene and then kept at room temperature and 80 °C for 4 h. The *E*/*Z* ratio of **1a** was determinted by ^{1}H NMR, and the results indicated that the *E*/*Z* ratio after heating (*E*:*Z* > 99:1) was consistent with that at room temperature (*E*:*Z* > 99:1). This proved that the *E* → *Z* isomerization of substrate **1a** can not be achieved by thermodynamic conversion.

To explore the mechanism of the overall reaction, the model reaction was kept under dark conditions for 12 h, and product **2a** was obtained with 86% yield (Scheme 4b). Then, the model reaction was carried out at 0 °C, and extending the reaction time to 20 h can also obtain the desired product **2a** with high yield. The above results indicated that the reactions did not

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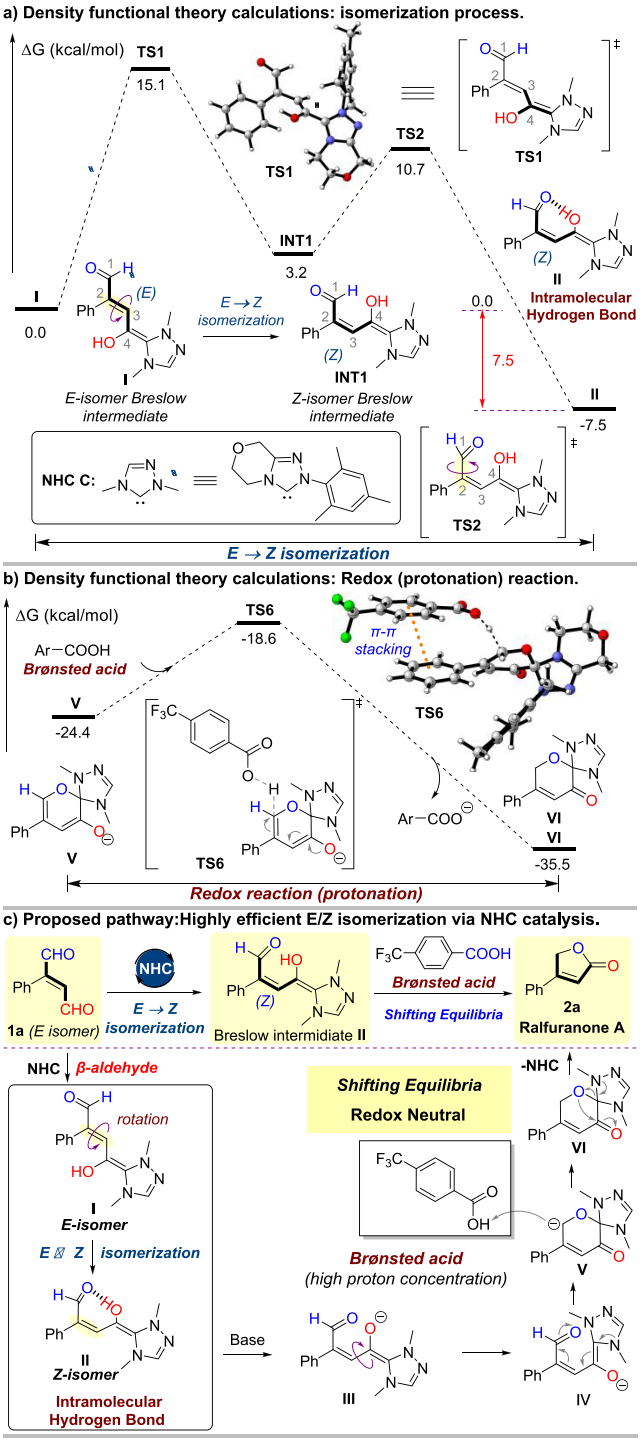
rely on the participation of light or heating. The background reaction without NHC catalyst was also investigated; the desired product could not be found after almost 3 days, and the **1a** recovery rate was 93%. It was worth noting that the *E*/*Z* ratio of remaining **1a** has not changed (*E*/*Z* > 99:1). In addition, the *E* → *Z* isomerization was exlpored without Brønsted acid. After 30 h, product **2a** could be clearly monitored by TLC. Then, the remaining **1a** was isolated, and the *E*/*Z* ratio changed to 16:1 determined by ^{1}H NMR. These results suggested that the *E* → *Z* isomerization occurred after NHC reacted with substrate **1a**. Meanwhile, the shifting equilibria can not be moved forward effectively without Brønsted acid. These two cascade processes ensured smooth progress of overall NHC-catalyzed cycloaddition reactions.

To understand the mechanism of the new *E*/*Z* isomerization catalytic mode, density functional theory (DFT) calculations were performed (Scheme 5). (See SI for the computational details). First, the C_2═C_3 double bond rotational barrier of the substrate **1a** was calculated; it was found that the energy barrier was very high ($\Delta G^{\ddagger}$ = 44.4 kcal/mol), while it was difficult to achieve the *E* → *Z* isomerization under mild conditions. *E*-Isomer Breslow intermediate **I** was chosen as the starting point, which was obtained by the reaction of NHC **C** and enedial **1a**. *E*-isomer Breslow intermediate **I** underwent *E* → *Z* isomerization around the C_2═C_3 double bond with a greatly reduced energy barrier of only $\Delta G^{\ddagger}$ = 15.1 kcal/mol to form intermediate **INT1**. This was much lower than the energy barrier for direct rotation of the C_2═C_3 double bond in **1a**. Then, the unstable intermediate **INT1** underwent a low-barrier conformational reorganization (ΔG = 7.5 kcal/mol), where the rotation of the C_1−C_2 single bond enabled the formation of an intramolecular hydrogen bond between the enol and aldehyde in Breslow intermediate **II** to greatly stabilize the conformation (Δ*G* = −7.5 kcal/mol). This process was highly thermodynamically favorable. Then, intermediate **V** can be generated via the conformational adjustment and cycloaddition.[63,64] Subsequently, intermediate **V** will be protonated easily by the Brønsted acid to generate the intermediate **VI**. A *π*-*π* stacking between acid and substrate may stabilize **TS6** and promote the shifting equilibria. The overall Gibbs energy profile gave the energetic span as −45.1 kcal/mol for the formation of the desired product **2a** (See SI for the complete Gibbs Profile).

Based on these mechanism studies, a possible mechanism was proposed (Scheme 5c). Above all, the *E*-isomer substrate **1a** was reacted with NHC **C** to generate the corresponding *E*-isomer Breslow intermediate **I** smoothly, and the rotational energy barrier of the C═C double bond in Breslow intermediate **I** was significantly reduced. Therefore, *Z*-isomer Breslow intermediate **II** was obtained. Moreover, an intramolecular hydrogen bond was formed in intermediate **II**, which can largely stabilize the structure. The above process completed the *E* → *Z* isomerization and laid the foundation of overall reactions. Then, through a deprotonation reaction and conformational adjustment, the intermediate **V** can be given. Brønsted acid greatly increased the proton concentration, which also can be used as an oxidant to accelerate the conversion of intermediate **V** to **VI** through the shifting equilibria. The whole redox-neutral reaction process achieved the cascade reaction of contra-thermodynamic *E* → *Z* isomerization and intramolecular esterification, and the product **2a** can be obtained with high yield.

In summary, we have reported a NHC-catalyzed and Brønsted acid copromoted *E* → *Z* isomerization mode which

Scheme 5. Highly Efficient *E*/*Z* Isomerization Mode[a]



[a]Gibbs energies are computed at the IEFPCM (DCM)-M06-2X-D3/def2-TZVPP//IEFPCM(DCM)-M06-2X-D3/def2-SVP level of theory and are quoted in kcal/mol.

enables the synthesis of ralfuranones. The *E* → *Z* isomerization via NHC catalyst and the lactone formation reaction promoted by the Brønsted acid were the two key steps. *E*-Isomer Breslow intermediates were generated through the reaction of *E*-isomer enedials with the NHC catalyst. The rotational energy barrier of the C═C double bond in the Breslow intermediate was reduced and stabilized the structure via intramolecular hydrogen bonding. Meanwhile, the Brønsted acid promoted

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the redox-neutral reaction. Through the $E \rightarrow Z$ isomerization and shifting equilibria, ralfuranone containing a Z-type C=C double bond was obtained. The desired products from our reactions can be readily converted to various Z-type C=C double bond containing compounds. The new efficient $E \rightarrow Z$ isomerization mode, catalyzed by NHC and promoted by Brønsted acid, provides a promising approach for synthesizing single geometric isomers and can be further applied to the development of new catalytic transformations.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c01033.

Experimental procedures, optimization of reaction conditions, compounds characterization, crystal data, computational study and copies of NMR spectra (PDF)

Accession Codes

Deposition Number 2391932 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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