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Regiospecific Ficini [2 + 2] Cycloaddition of Ynamides with Cyclic Isoimidium Salts under Catalyst-Free Conditions

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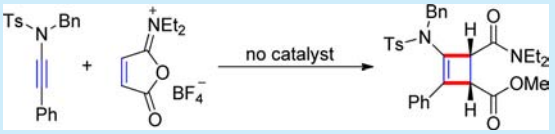
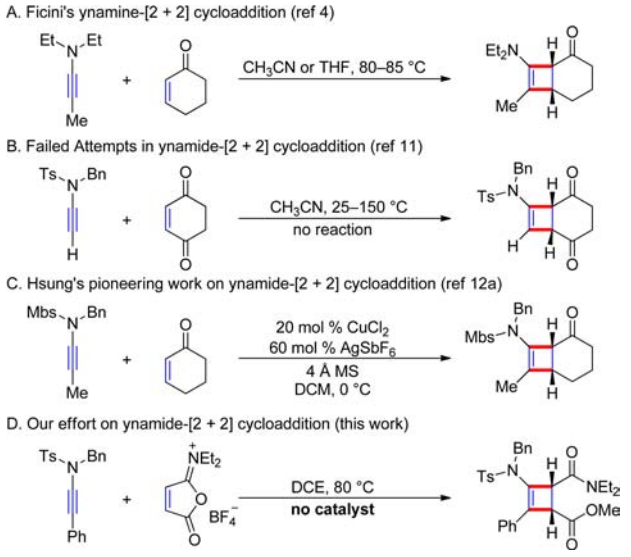
Supporting Information

ABSTRACT: The regiospecific [2 + 2] cycloaddition of cyclic isoimidium salts with ynamides is described. This effort led to the development of the first successful example of a catalyst-free, thermally driven Ficini [2 + 2] cycloaddition process of ynamides with α,β-unsaturated carbonyl compounds, giving the stable cyclobutenamides in excellent yields (up to 99%).



Four-membered rings are important structural motifs, being frequently found in natural products and biologically active compounds.[1] As a result, great efforts have been devoted to developing more efficient methods to access these valuable scaffolds.[2] For example, Ficini reported a catalyst-free, thermally driven stepwise [2 + 2] cycloaddition of ynamines with electron-deficient enones to give cyclobutenamine products (Scheme 1A).[3,4] However, the synthetic application of this protocol has been dramatically limited, which is mainly due to the difficulties of preparing, handling, and storing a wide spectrum of highly functionalized ynamines.[5] To circumvent the problem associated with the poor stability of ynamines, ynamides which are attached with electron-withdrawing carbonyl/sulfonyl groups on the nitrogen have turned out to be superior alternatives.[6] Notably, several [2 + 2] cycloaddition reactions combining ynamides with strained bicyclic alkenes,[7] ketenes,[8] carbonyl compounds,[9] and imines[10] have been successfully discovered. However, tremendous attempts at the development of [2 + 2] cycloaddition in a Ficini manner using ynamides under thermal conditions have unfortunately failed (Scheme 1B).[11] Due to the high stability of ynamides, the successful achievements in this area were rendered by the incorporation of transition-metal Lewis acids (Cu, Ag, Ru, and Rh) very recently.[12] Elegant examples include the first report by Hsung featuring the utility of $CuCl_2$ and $AgSbF_6$ as the catalysts (Scheme 1C),[12a] the enantioselective Ru-catalyzed variant with cyclic unsaturated β-ketoesters by Mezzetti,[12b−d] and the Rh-catalyzed [2 + 2] cycloaddition of yanamides with nitroalkenes reported by Lam.[12e] In order to establish a greener catalyst-free Ficini reaction by employing ynamides, we switched gears to utilize other types of more reactive α,β-unsaturated carbonyl compounds in comparison to the previously studied electron-deficient alkenes. Herein, we present the first successful example of a catalyst-free, thermally driven Ficini [2 + 2] cycloaddition of ynamides with α,β-unsaturated carbonyl compounds (Scheme 1D).

Scheme 1. Historical Development of Ficini Reaction



During our search for more reactive and easily handled α,β-unsaturated carbonyl compounds to enable the [2 + 2] cycloaddition with ynamides under Ficini thermal conditions, we were attracted to the cyclic isoimidium salts. These bench-stable crystalline salts were first synthesized by the Boyd group in an environmentally benign fashion from inexpensive maleic anhydride and diethylamine.[13] Notably, the same group also demonstrated that these salts could serve as potent acylating agents for nucleophilic amines, alcohols, azides, and aromatic compounds in a regiospecific fashion to give the corresponding ring-opened products. However, to our surprise, the potential of using these electron-deficient olefinic salts in cycloaddition reactions was not evaluated until very recently.[14] Remarkably, these salts were then proven to be extremely effective dienophiles for a regiospecific Diels−Alder transformation

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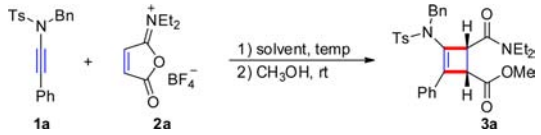
under catalyst-free conditions. Taking this discovery into account, we hypothesized that the cyclic isoimidium salts could undergo a [2 + 2] cycloaddition reaction with more stable ynamides to generate cyclobutenamide products.

At the outset, our study started with taking ynamide **1a** and isoimidium tetrafluoroborate salt **2a** as the model substrates to examine the reaction conditions (Table 1). First, a series of

Table 1. Screen of the Reaction Conditions



1a 2a 3a

entry	solvent	concn (M)	temp (°C)	yield (%)[a]
1	DCE	0.5	40	70
2	DCM	0.5	40	68
3	CH_3CN	0.5	40	45
4	dioxane	0.5	40	33
5	toluene	0.5	40	<5
6	THF	0.5	40	NR
7	DCE	0.5	80	83
8	DCE	0.25	80	72
9	DCE	0.75	80	86
10	DCE	1.0	80	92

[a]Isolated product after purification.

solvents including DCE, DCM, CH_3CN, 1,4-dioxane, toluene, and THF were screened, and DCM and DCE provided the better results, giving desired product **3a** in moderate yields (entries 1−2). Accordingly, the isoimidium tetrafluoroborate salt **2a** exhibited superior solubility in nonpolar organic solvents such as DCE and DCM, so that might be the reason why these solvents could promote the reactions more effectively. Next, the reaction temperature was elevated to 80 °C, and the yield of **3a** was improved to 83% (entry 7). Finally, the optimal result was obtained by increasing the reaction concentration to 1.0 M (entry 10). Overall, the [2 + 2] cycloaddition reaction between **1a** and **2a** could proceed smoothly in DCE at 80 °C without adding any catalyst, generating cyclobutenamide **3a** as the product in excellent yield (92%). Notably, the control experiments using maleic anhydride to replace **2a** in the title reaction could not produce the [2 + 2] cycloaddition product under various thermal conditions. According to NMR spectroscopy, compound **3a** was formed as a single regioisomer, which was unambiguously assigned by X-ray studies (Figure 1).

With the optimal reaction conditions in hand, we sought to examine the scope of this transformation. Thus, an important number of ynamides with different steric and electronic properties were synthesized and tested with this newly established [2 + 2] cycloaddition procedure. As summarized in Scheme 2, all tested ynamides reacted with isoimidium tetrafluoroborate salt **2a** regiospecifically to generate a broad range of cyclobutenamides (**3a**−**o**) in high yields (83−99%). With regards to the substituents on the terminal position of the alkynes, various electron-rich and -poor aromatic (**3b** and **3c**), heterocyclic (**3d**−**e**), olefinic (**3f**), and aliphatic (**3g**−**h**) groups were well tolerated. The studies were then carried out by varying the substituents on the nitrogen atom, and it was found that the benzyl substituent on the nitrogen could be replaced with alkyl groups such as *n*-butyl and allyl, affording cyclobutenamides (**3i**−**k**) in good yields. Next, the electron-

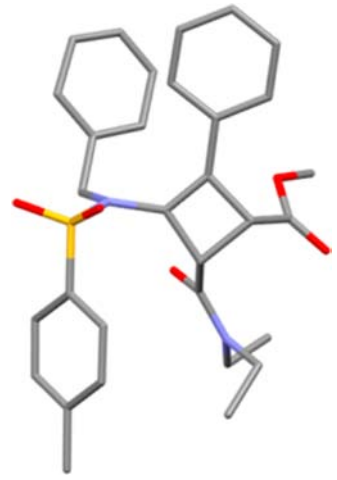
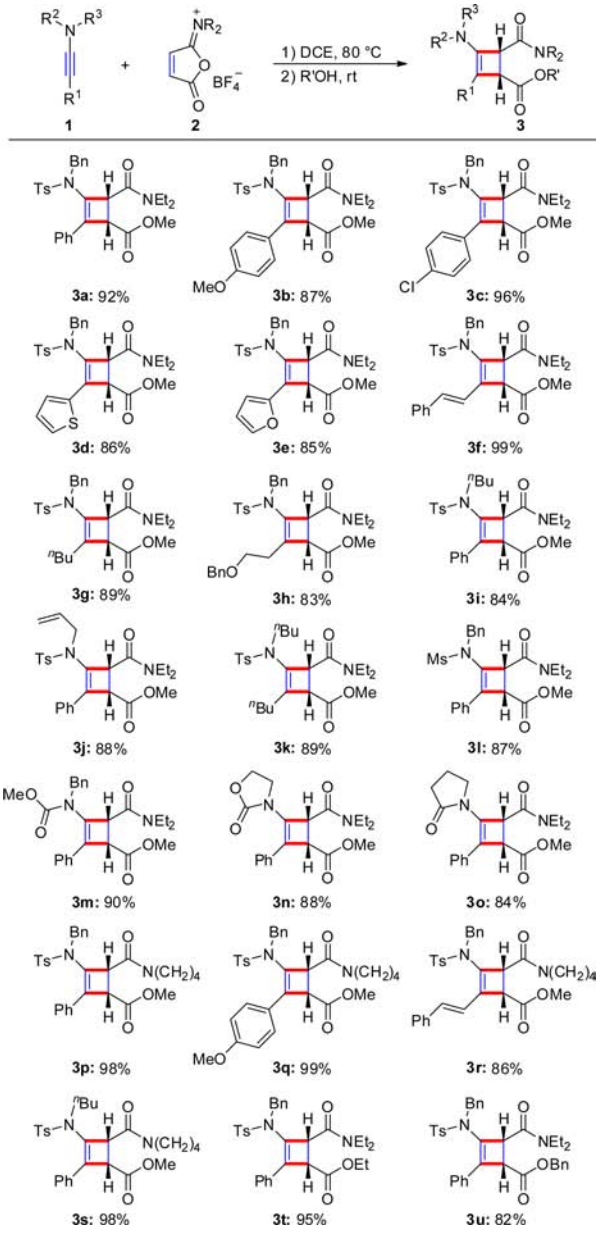


Figure 1. X-ray structure of the [2 + 2] cycloadduct **3a**.

Scheme 2. Investigation of the Reaction Scope



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withdrawing group on the nitrogen does not need to be Ts, and it could be changed with Ms (**3l**). Besides Ts and Ms groups, which are not easily removed, carbonyl groups derived from carbamate, oxazolidinone and pyrrolidinone, could be incorporated as the electron-withdrawing group for the ynamides as well. It is noteworthy that previous attempted reactions between this type of ynamides and unsaturated carbonyl compounds were unsuccessful under different conditions.[11,12a] In contrast, the [2 + 2] cycloaddition reactions between these ynamides and **2a** proceeded smoothly under our standard reaction conditions, giving their corresponding products (**3m**, **3n**, and **3o**) in 90%, 88%, and 84% yields, respectively. In further studies, the isoimidium tetrafluoroborate salt **2b** based on pyrrolidinone was also proven to be a suitable reaction partner for different ynamides to provide compounds **3p**–**s** in 86–98% yields. For the second step of the transformation, ethanol and benzyl alcohol appeared to show similar activity as methanol for opening the five-membered ring of the intermediate from the first step, with the formation of **3t** and **3u** as the products.

A notable result was observed when a TBS protecting ynamide **1v** was reacted with the isoimidium salt **2a**. Compound **3v′** was obtained as the single product in 94% yield, and its structure was ambiguously confirmed by X-ray crystallography studies (Figure 2). The possible reaction

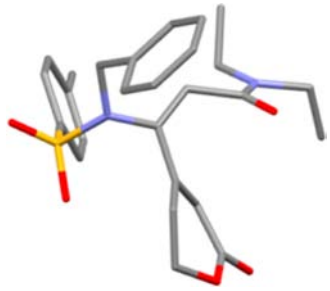
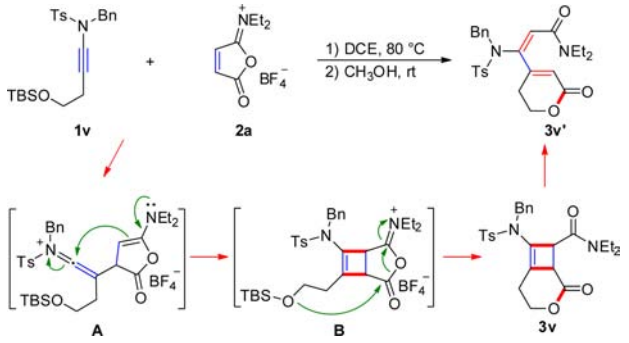


Figure 2. X-ray structure of compound **3v′**.

Scheme 3. Formation of Compound 3v′ from 1v and 2a



pathway is depicted in Scheme 3. Accordingly, the expected [2 + 2] transformation should undergo a stepwise cycloaddition process with a regiospecific attack by the ynamide **1v** onto the electrophilic *β*-position of the iminium species in **2a**, and then followed by enamine–iminium coupling to give **B**. Next, a six-membered ring was presumably formed by TBS deprotection and lactone cyclization, thus furnishing bicyclic **3v**. In the final step, the observed product **3v′** was generated by a retro-electrocyclization in a stereospecific fashion.[15]

In summary, we described the first catalyst-free Ficini [2 + 2] cycloaddition reaction with ynamides. The success of the process relies on the incorporation of cyclic isoimidium salts as the electron-deficient alkene reaction partner, resulting in a range of cyclobutenamide products in a regiospecific manner in high yields.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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