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Ytterbium-Catalyzed Intramolecular [3 + 2] Cycloaddition based on Furan Dearomatization to Construct Fused Triazoles

Xiaoming Xu, Ying Zhong, Qingzhao Xing, Ziwei Gao, Jing Gou,* and Binxun Yu*

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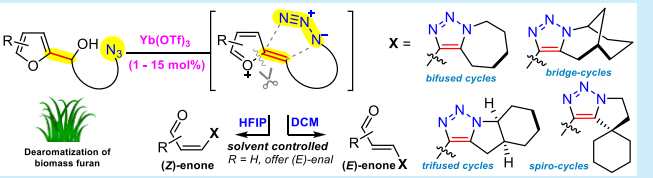
ABSTRACT: The 1,2,3-triazole-containing polycyclic architecture widely exists in a broad spectrum of synthetic bioactive molecules, and the development of expeditious methods to synthesize these skeletons remains a challenging task. In this work, the catalytic cyclization of biomass-derived 2-furylcarbinols with an azide to form fused triazoles is described. This approach takes advantage of a single catalyst $Yb(OTf)_3$ and operates via a furfuryl-cation-induced intramolecular [3 + 2] cycloaddition/furan ring-opening cascade.



The fused 1,2,3-triazole represents one of the privileged scaffolds in medicinal chemistry.[1−5] The preparation and creation of such skeletally related triazoles is of high synthetic and biological interest. Herein we described a novel catalytic synthesis of a fused triazole from the azido furylcarbinol adducts, employing a $Yb(OTf)_3$-catalyzed intramolecular [3 + 2] cycloaddition/furan ring-opening cascade reaction.

The most straightforward protocol to access the fused 1,2,3-triazoles is via the intramolecular 1,3-dipolar cycloaddition of azides and alkynes, which typically involves a high temperature of >100 °C under metal-free conditions (Scheme 1a).[6] The intramolecular Cu(I) or other transition-metal-catalyzed [3 + 2] cycloaddition of azides with alkynes, which is often called a "click reaction", is capable of synthesizing the fused 1,2,3-triazoles under mild conditions.[7] Several modifications have been disclosed to give the fused 1,2,3-triazoles via the metal-catalyzed intramolecular C−C coupling or the C−H activation strategies of the triazole moiety, which must be primarily constructed by means of the click reaction.[8] However, the cytotoxicity of the transition metal could represent a crucial drawback for pharmaceutical applications, and the development of transition-metal-free protocols remains a continuous challenge for synthetic chemists. In fact, organocatalytic methods have been developed, which basically involve a base-mediated cycloaddition/elimination cascade between a polar methylene adduct with an azide to access fused 1,2,3-triazoles.[9]

Biomass-derived furan is a vital synthetic tool due to its low aromaticity.[10] Not only can it perform as latent alkenes, enol ethers,[11] 1,4-diketones,[12] and carboxylic acids[13] but also it normally enables facile recyclizations into various carbo-[14−16] and heterocycles.[17,18] Recently, a complementary triazole synthesis directly from readily available furan derivatives was developed by our group (Scheme 1b).[19] This methodology involves an intermolecular [3 + 2] cycloaddition between a 2-furylcarbinol and an organo azide to form triazoles and a subsequent furan ring-opening to give enone motif. However, the major issue is that stoichiometric aggressive Lewis acids, such as $TiCl_4$ or $SnCl_4$, were applied. They are environmentally

Scheme 1. Representative Methods for Fused Triazole Synthesis in Comparison with the Present Work

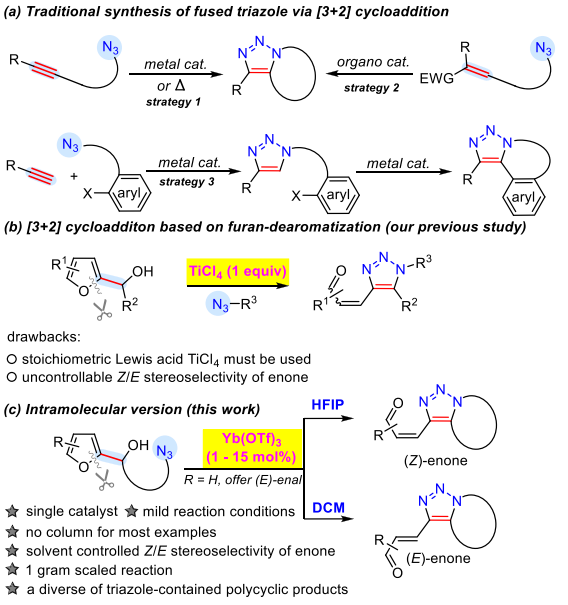


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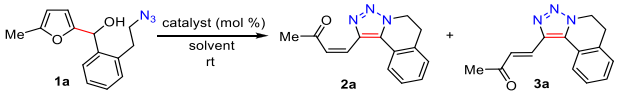
Table 1. Catalyst Screen for Intramolecular [3 + 2] Cycloaddition Reaction



entry[a]	catalyst (mol %)	solvent/time (h)/temp (°C)	yield of **2a** (%)[b]	yield of **3a** (%)[b]
1	$In(OTf)_3$ (5)	CH_2Cl_2/5/40		86
2	$Dy(OTf)_3$ (5)	CH_2Cl_2/5/40		82
3	$Sc(OTf)_3$ (5)	CH_2Cl_2/5/40		89
4	**$Yb(OTf)_3$ (5)**	**CH_2Cl_2/5/40**		**95**
5	$La(OTf)_3$ (5)	CH_2Cl_2/5/40		80
6	$In(OTf)_3$ (5)	HFIP/1/0−rt	87	
7	$Dy(OTf)_3$ (5)	HFIP/1/0−rt	85	
8	$Sc(OTf)_3$ (5)	HFIP/1/0−rt	90	
9	$La(OTf)_3$ (5)	HFIP/1/0−rt	84	
10	**$Yb(OTf)_3$ (5)**	**HFIP/1/0−rt**	**98**	
11	$Yb(OTf)_3$ (2)	HFIP/1/0−rt	91	

[a]Conditions: azido furfurylcarbinol **1a** (0.2 mmol), solvent (1.0 mL). [b]Isolated yield; *Z*/*E* configuration were determined by ^1H NMR. HFIP, hexafluoroisopropanol.

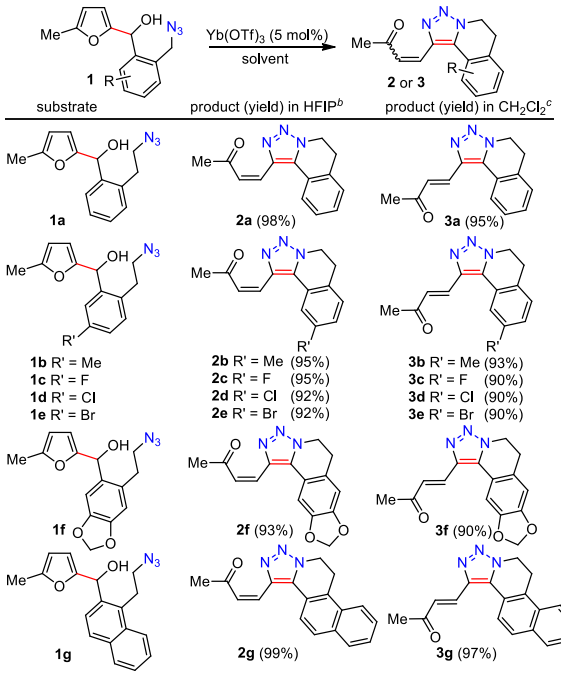
unfriendly, owing to their extreme moisture/air sensitivity and generation of metal-salt waste. The reaction often poses significant handling risks and workup dilemmas and suffers from poor yields when scaled up. Hence, our efforts focused on exploring a stable and environmentally friendly catalytic condition to realize the intramolecular [3 + 2] cycloaddition of 2-furylcarbinols and azides while avoiding the use of a stoichiometric transition-metal reagent to efficiently establish the fused triazole systems (Scheme 1c).

In our initial trials, the azido furfurylcarbinol adduct **1a** was employed to optimize the reaction conditions, and the results are summarized in Table 1. To our delight, the intended fused-triazole product **3a** was obtained in good yield in CH_2Cl_2 with the use of 5 mol % $In(OTf)_3$, $Dy(OTf)_3$, and $La(OTf)_3$ in 5 h at 40 °C (entries 1, 2, and 5). The configuration of enone was detected to be E. $Sc(OTf)_3$ provided a little improvement in yield (entry 3). Markedly optimized results were obtained with catalytic $Yb(OTf)_3$ in 95% yield (entry 4). Using the strong hydrogen-bond-donating solvent hexafluoro-2-propanol (HFIP) effectively accelerated this furan recyclization, in which the reaction was completed in 1 h at room temperature by utilizing 5 mol % catalysts. Importantly, the resulting product was **2a**, which furnished a *Z*-enone. The E-isomer was not observed in this reaction. $Yb(OTf)_3$ was identified as a superior agent and afforded a 98% yield (entry 10). When the catalyst loading was decreased to 2 mol %, the yield was slightly reduced (entry 11).

The optimized conditions with $Yb(OTf)_3$ in CH_2Cl_2 and HFIP, respectively (Table 1, entries 4 and 10), were then applied to the intramolecular [3 + 2] cyclization (Scheme 2). Substrates containing aromatic substituents with electron-rich (**1b**) or electron-poor (**1c**−**e**) character were tolerated and underwent the desired cascade reaction to give [6,6,5]-fused tricyclic products **2b**−**e** and **3b**−**e** in 90−95% yields. With the acid-sensitive substrate **1f** containing an acetal group, which was undisturbed, the yields of **2f** and **3f** were excellent. The reaction of naphthyl adduct **1g** occurred to afford **2g** and **3g** in brilliant yields. Gratifyingly, the exclusive Z- or E-configurations were observed for these products.

Subsequently, we studied the furan scaffold scope (Scheme 3). *n*-Pentyl-substituted furan **1h** was found to work well and afforded the corresponding products **2h** and **3h** in high yields with exclusive Z/E selectivities. 4,5-Dimethyl furfurylcarbinol

Scheme 2. Benzylic Alcohol Scope[a]



[a]Conditions: azido furfurylcarbinol **1** (0.2 mmol), 10 mL sealed tube. [b]$Yb(OTf)_3$ (0.01 mmol), HFIP (1 mL), 0 °C−rt, 1 h. [c]$Yb(OTf)_3$ (0.01 mmol), CH_2Cl_2 (1 mL), 40 °C, 5 h.

1i gave trisubstituted enones **2i** in 92% yield under the conditions of $Yb(OTf)_3$ in HFIP. However, a 1:1 mixture of **3i** and **2i** was generated in 90% total yield when the condition was changed to CH_2Cl_2. Meanwhile, the reaction needed to be heated to 100 °C. Interestingly, adduct **1j** without any substituent on the C-5 position of furan afforded the trans product **2j** in both CH_2Cl_2 and HFIP, which might be caused by the higher reactivity of the resulting conjugated aldehyde compared with the previously mentioned ketones.

Encouraged by the success of with the synthesis of fused benzo triazoles, aliphatic azide adducts were then investigated, giving the results summarized in Scheme 4. The reactions of a variety of aliphatic azides containing furfurylcarbinols proceeded smoothly under the standard conditions to afford

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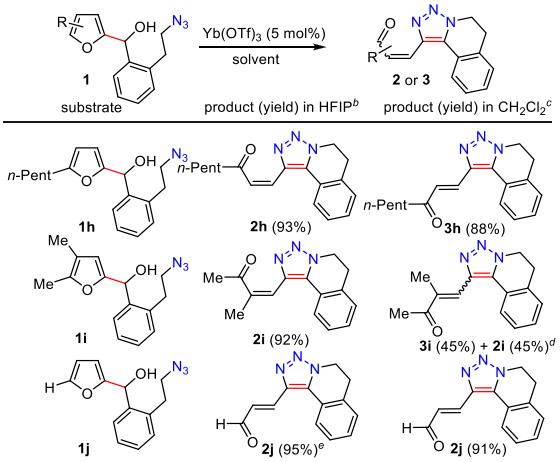
Scheme 3. Furan Scaffold Scope[a]

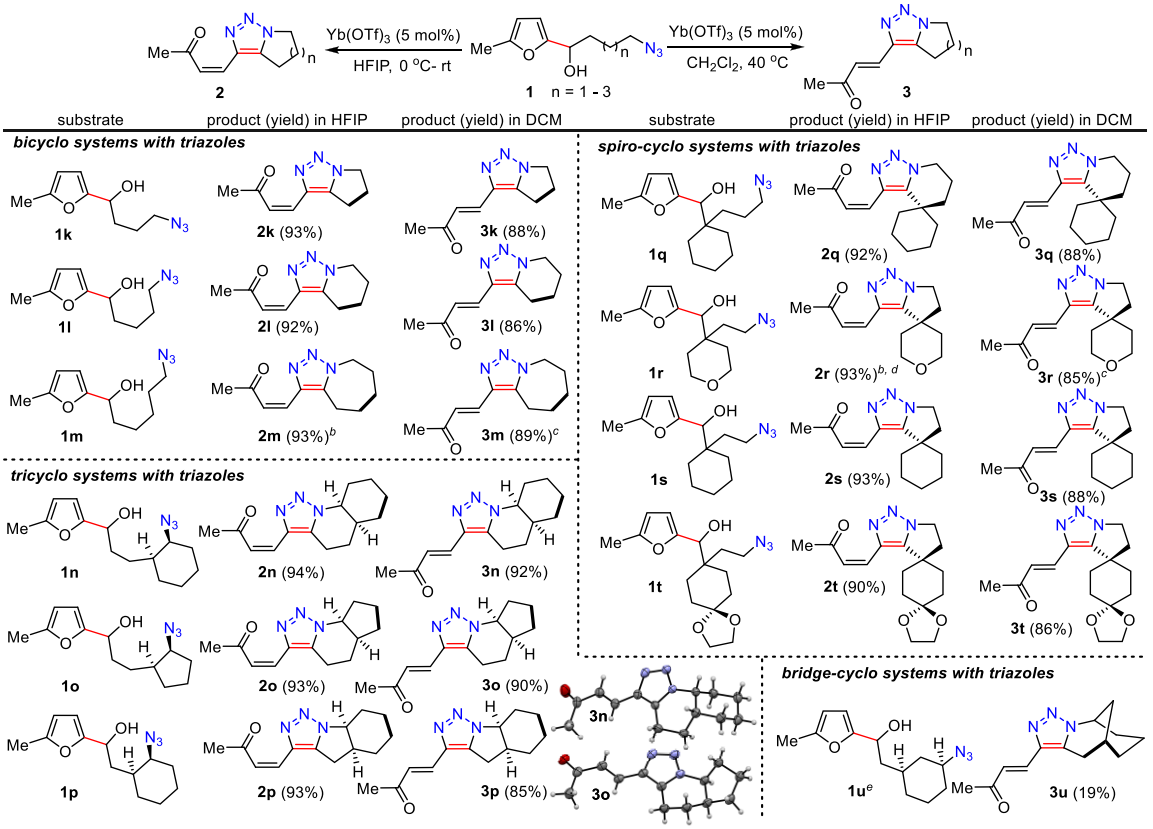


[a]Conditions: azido furfurylcarbinol **1** (0.2 mmol), 10 mL sealed tube. [b]$Yb(OTf)_3$ (0.01 mmol), HFIP (1 mL), 0 °C−rt, 1 h. [c]$Yb(OTf)_3$ (0.01 mmol), CH_2Cl_2 (1 mL), 40 °C, 5 h. [d]Reaction needed to be heated to 100 °C and afforded a mixture of **2i** and **3i** (1:1).

the corresponding [5,5], [5,6], and [5,7] bicyclo triazoles **2k**, **3k**, **2l**, **3l**, **2m**, and **3m** in excellent yields with great Z/E selectivities. When the secondary azides were fixed on the cyclopentane or cyclohexane (**1n−p**), the more complex [5,6,6], [5,6,5], and [5,5,6] tricyclo triazoles **2n**, **3n**, **2o**, **3o**, **2p**, and **3p** were obtained. X-ray diffraction analysis further confirmed the structures of **3n** (CCDC no.1965895) and **3o** (CCDC no.1965896). The cyclo substrates **1q−s** containing a quaternary azide side chain can be used to carry out the reactions and afforded the desired spiro systems **2q**, **3q**, **2r**, **3r**, **2s**, and **3s** in decent yields. Spiro ketal compound **1t** was also found to be compatible with the reaction conditions, giving the cycloaddition products **2t** and **3t** in 90 and 86% yields, respectively. It is worth noting that most of the previously mentioned reaction systems can provide pure enough NMR spectra of desired products after regular workup without further purification, indicating the excellent conversion of this new transformation. The transannular [3 + 2] cycloaddition of furfurylcarbinol with a secondary azide reacted, delivering the bridge triazole **3u** with great Z/E selectivities in CH_2Cl_2, but it gave a low yield of 19%. Unfortunately, the reaction in HFIP generated a complicated unidentified mixture, and the desired Z-product could not be observed.

To gain a deeper insight into the Z/E stereoselectivities in two different solvents, we monitored the reaction of azido furfurylcarbinol **1a** in CD_2Cl_2 (0.1 M) by *in situ* ^1H NMR (Figure 1). The conversion of **1a** could not be found at room temperature in 5 min. When the sample in NMR tube was heated to 40 °C, the ^1H NMR signals of *Z*-*β*-triazole-enone **2a** were observed, along with the consumption of **1a** within 30 min and 60% conversion within 50 min. The formation of the appreciable E-product **3a** was observed within 110 min; then, **1a** totally disappeared within 130 min. The isomerization of **2a**

Scheme 4. Various Fused Triazoles[a]



[a]Conditions: azido furfurylcarbinol **1** (0.2 mmol), $Yb(OTf)_3$ (0.01 mmol) for HFIP (1 mL) under 0 °C in 1 h, or $Yb(OTf)_3$ (0.01 mmol) for CH_2Cl_2 (1 mL) under 40 °C in 5 h, 10 mL sealed tube. [b]Reaction time was prolonged to 8 h. [c]Under 60 °C. [d]$Yb(OTf)_3$ (0.03 mmol) was used. [e]Reaction afforded an unidentified mixture in HFIP, and no desired Z-product was observed.

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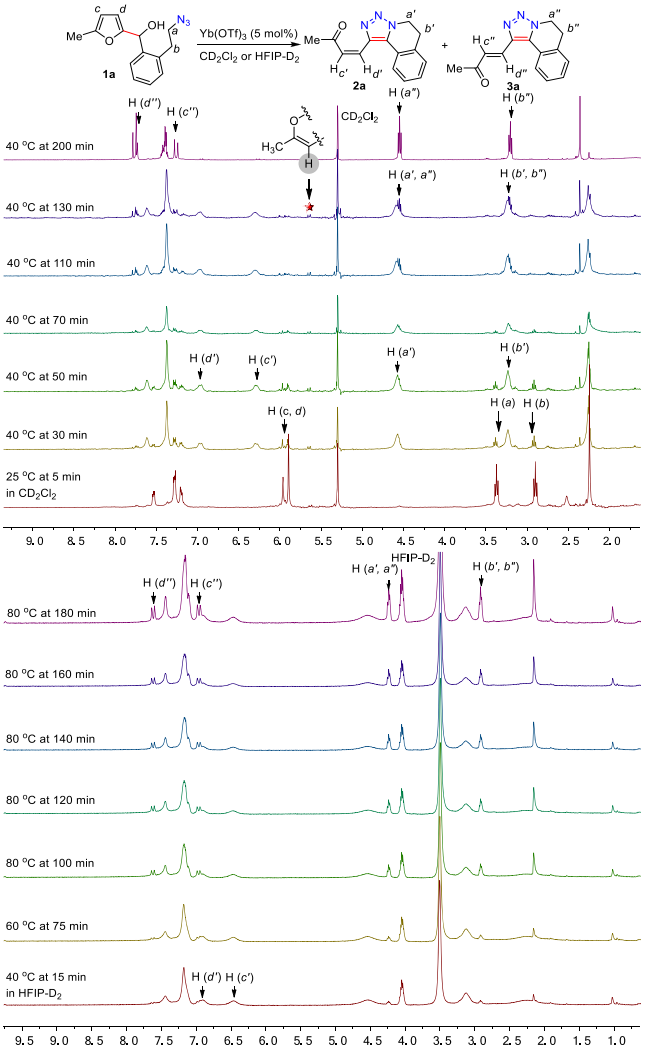


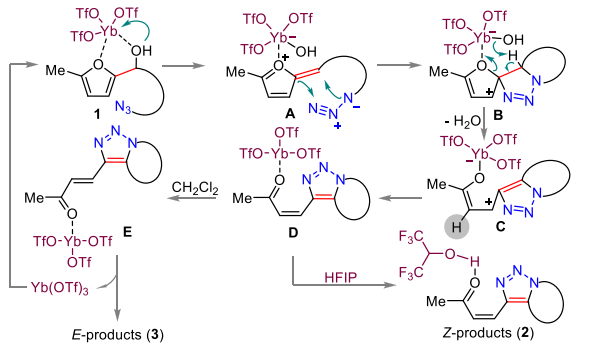
Figure 1. *In situ* ^{1}H NMR study of the reaction of **1a** (0.1 M, CD_2Cl_2, and HFIP-D_2).

continually occurred, and full conversion was observed after 200 min, affording pure ^{1}H NMR spectra of E-product **3a**.

Then, we probed the solvent effects of the reaction in HFIP-D_2 through *in situ* ^{1}H NMR and found that the conversion of **1a** into the desired **2a** was quickly accomplished within 15 min at 25 °C. Although the reaction temperature was successively elevated to 40 and 60 °C for 60 min, Z-product **2a** was still stable, and the ^{1}H NMR signals of **3a** could not be observed. The isomerization of **2a** was detected until the temperature was elevated to 80 °C, and only a 50% conversion of **2a** into **3a** was reached at 180 min. Therefore, the results indicated that E-products are produced by the thermodynamic isomerization of Z-products under the condition of CH_2Cl_2 rather than being directly generated from adducts. Furthermore, HFIP is capable of stabilizing the Z-configuration of *β*-triazole-enone, inhibiting its isomerization into the thermodynamically more favored E-configuration at ambient temperature.

On the basis of the above experimental findings, a plausible mechanism is proposed in Scheme 5. The initial step involves the Yb(OTf)$_3$-mediated dehydroxylation of azido furfurylcarbinol **1** to furnish furfuryl cation **A**,[24] which could react with the azide group via an intramolecular formal [3 + 2] cycloaddition to give the spiro cation **B**. The aromatization

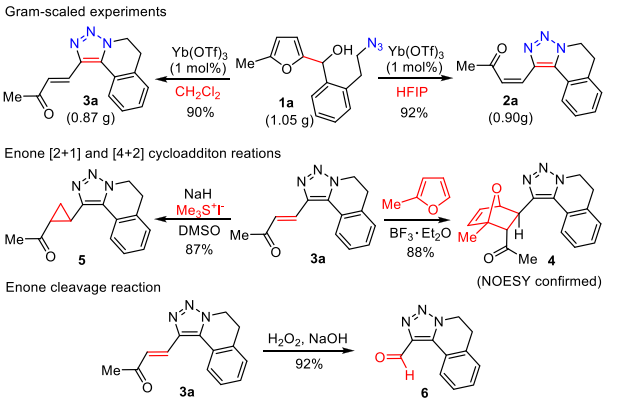
Scheme 5. Proposed Reaction Mechanism



of **B** generates triazole, and the subsequent ring-opening of furan delivers the enolate **C**, which has been observed in *in situ* NMR studies. A further tautomerization gives **D**. Of note, in CH_2Cl_2, the ytterbium catalyst coordinated with the oxygen atom of *the* Z-enone group could activate the conjugated double bond and lead to the occurrence of the isomerization from the Z-configuration to the thermodynamically more favorable E-configuration. The intermediate **E** undergoes the dissociation of Yb(OTf)$_3$ to afford desired E-product **3**. The high dielectric constant (ε = 15.7) and low nucleophilicity mean that HFIP is an ideal solvent in which to generate and study cations.[20] The strong effects of HFIP on the stabilization of allyl[21] and benzylic[22] cations with nucleophiles have been proven. When the Yb-catalyzed reaction is run in HFIP medium, it is feasible that furfuryl cation **A** benefits from the stabilized effects, and a significant acceleration has been observed compared with the reaction in CH_2Cl_2. Moreover, after generating **D**, a fast exchange of the catalyst with HFIP could occur, finally giving Z-product **2**. The relatively low acidity of HFIP could not result in the further isomerization of double bonds.[23]

To test the practicality of this methodology, the gram-scale reactions using **1a** as a substrate were carried out (Scheme 6).

Scheme 6. Further Transformations



Pleasingly, the catalyst Yb(OTf)$_3$ can be reduced to 1 mol %, providing **2a** and **3a** in 92 and 90% yields in CH_2Cl_2 and HFIP, respectively. Additionally, to demonstrate the utility of the products, further manipulation reactions were conducted. For example, the Diels−Alder reaction of **3a** with 2-methyl furan under BF_3·Et_2O as the Lewis acid proceeded smoothly to provide **4** in 88% yield, whereas the Corey−Chaykovsky reaction of **3a** was performed to give cyclopropane **5** in 87%

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yield. Interestingly, we found that the oxidative cleavage of the double bond of **3a** can be achieved with a mild condition of H_2O_2/NaOH, offering the fused triazole aldehyde **6** in 92% yield.

In conclusion, we have developed a $Yb(OTf)_3$-catalyzed intramolecular [3 + 2] cycloaddition of furfurylcarbinols with azides to devise complex enone triazoles with diverse fused cyclic patterns. The excellent yields of products can be achieved by low catalyst loading, even reducing to 1 mol % to accomplish the full conversion of a gram-scaled reaction. Notably, the catalytic reaction is capable of providing the high Z/E selectivity of enones by the judicious choice of CH_2Cl_2 or HFIP solvents. Studies focused on the detailed mechanistic aspects, the synthetic scope, and the applications of this reaction are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01780.

Experimental procedures, product characterization, copies of NMR spectra, and crystallographic data for **3n** and **3o** (PDF)

Accession Codes

CCDC 1965895−1965896 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Binxun Yu − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry & Chemical Engineering and Key Laboratory of Medicinal Resources and Natural Pharmaceutical Chemistry, Ministry of Education, College of Life Science, Shaanxi Normal University, Xi'an 710062, China;* orcid.org/0000-0001-8091-0669; Email: yubx@snnu.edu.cn

Jing Gou − *Shaanxi Key Laboratory for Advanced Energy Devices, Shaanxi Normal University, Xi'an 710062, China;* Email: goujing@snnu.edu.cn

Authors

Xiaoming Xu − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry & Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China*

Ying Zhong − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry & Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China*

Qingzhao Xing − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry & Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China*

Ziwei Gao − *Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry & Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China;* orcid.org/0000-0002-2547-9375

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01780

Notes

The authors declare no competing financial interest.

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