Lewis Acid Catalyzed Intramolecular Ring Opening of Triazole-Substituted Methylenecyclopropanes: An Approach to 4*H*-[1,2,3]Triazolopyrazines and 4*H*-[1,2,3]Triazolo[1,4]diazepines

Run Sun,[a] Di-Han Zhang,[b] Min Shi*[a,b]

[a] Key Laboratory for Advanced Materials and Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Mei-Long Road, Shanghai 200237, P. R. of China

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. of China
Fax +86(21)64166128; E-mail: mshi@mail.sioc.ac.cn

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Abstract: A series of novel methylenecyclopropane-triazoles have been successfully prepared. Their intramolecular nucelophilic cyclizations have been explored in the presence of $Yb(NTf_2)_3$ catalyst, giving the corresponding triazole containing six- and seven-membered heterocycles in good yields upon heating in toluene.

Key words: triazole, methylenecyclopropanes, Lewis acid, intramolecular cyclization

Methylenecyclopropanes (MCP), as highly strained but readily accessible molecules, have been important building blocks in organic synthesis for a long time[1] because they can undergo a variety of ring-opening reactions through the release of cyclopropyl ring strain (40 kcal/mol).[2] The strained energy can provide a thermodynamic driving force for reactions and the π-character of the bonds within the cyclopropane can afford the kinetic opportunity to initiate the ring opening.[3] Over the past few decades, several excellent review articles have been published on the transformation of these *exo*-methylene three-membered carbocycles.[4] Besides transition-metal catalysts, Lewis and Brønsted acids can be also used as catalysts or reagents in the reactions of MCP with a variety of substrates. It has been disclosed that substituents on the terminus of the double bond or cyclopropyl ring of MCP significantly affect the reaction pathways, and some interesting transformations have been found during the past decade by our group and others.

Several studies have focused on intramolecular nucleophilic addition of MCP bearing a nucleophilic group (Scheme 1). For example, our group and Huang's group reported the efficient stereoselective synthesis of bicyclo[3.1.0]hexane from the reaction of 2-substituted MCP with iodine (mode A, Scheme 1).[5] Lautens and co-workers studied the MgI_2-mediated ring expansions of secondary MCP amides, giving the isomeric five-membered unsaturated lactams in good yields (mode B, Scheme 1).[6] Ma and co-workers reported a regioselective palladium-catalyzed ring-opening cycloisomerization of MCP ketones (mode C, Scheme 1).[7] Moreover, gold(I)-catalyzed intramolecular hydroamination and ring opening of MCP has been disclosed by our group (mode D, Scheme 1).[8] On the basis of above achievements, we attempted to investigate the intramolecular nucleophilic addition of MCP bearing a nucleophilic group in which the nucleophile and MCP are tethered with a nitrogen atom in the presence of Lewis acid such as $Yb(OTf)_3$ or $Yb(NTf_2)_3$ (Scheme 1, this work). Therefore, we designed and synthesized a novel type of triazole-substituted MCP **1**, which contain a coordinative double bond, a strained carbocycle, and an additional triazole group. We envisioned that through an intramolecular hydroamination along with a C–C bond cleavage of the cyclopropane in the presence of Lewis acid, 4*H*-[1,2,3]triazolo[1,5-*a*]pyrazine derivative **2** and 4*H*-[1,2,3]triazolo[1,5-*a*][1,4]diazepine **3** could be formed. These products can be biologically interesting because several compounds bearing substituted triazolopyrazines have been used to treat type 2 diabetes by inhibiting dipeptidyl peptidase IV (DPP-4) such as *Sitagliptin*.[9]

Using MCP-triazole **1a** as substrate, we examined the reaction outcomes with a variety of Lewis acids in toluene at 110 °C. The results are summarized in Table 1. Using $BF_3{\cdot}OEt_2$ (10 mol%) as the catalyst afforded the desired products **2a** and **3a** in 38% yield with a 1:1.1 ratio (Table 1, entry 1). In the presence of $Ti(O\textit{i}\text{-}Pr)_4$, $FeCl_2$, $FeCl_3$, or Brønsted acid HOTf, complex product mixtures were produced under the standard conditions (Table 1, entries 2–5). Many triflated metal salts were more efficient catalysts in this reaction and we identified that $In(OTf)_3$, $In(NTf_2)_3$, and $Yb(NTf_2)_3$ were the most efficient catalysts in this reaction, affording **2a** and **3a** in >82% yield (Table 1, entries 6–18). Next, using $Yb(NTf_2)_3$ as the catalyst, we examined the solvent effects in DCE, THF, hexane, and MeCN, but no better result could be produced (Table 1, entries 19–22). Increasing the catalyst loading to 15 mol%, **2a** and **3a** were obtained in 89% yield in toluene within 12 hours, which are the best conditions for this reaction (Table 1, entry 23). Upon prolonging the reaction, the decomposition of the desired products was identified at 80 °C because complex product mixture was formed (Table 1, entry 24). The reaction did not give any desired products

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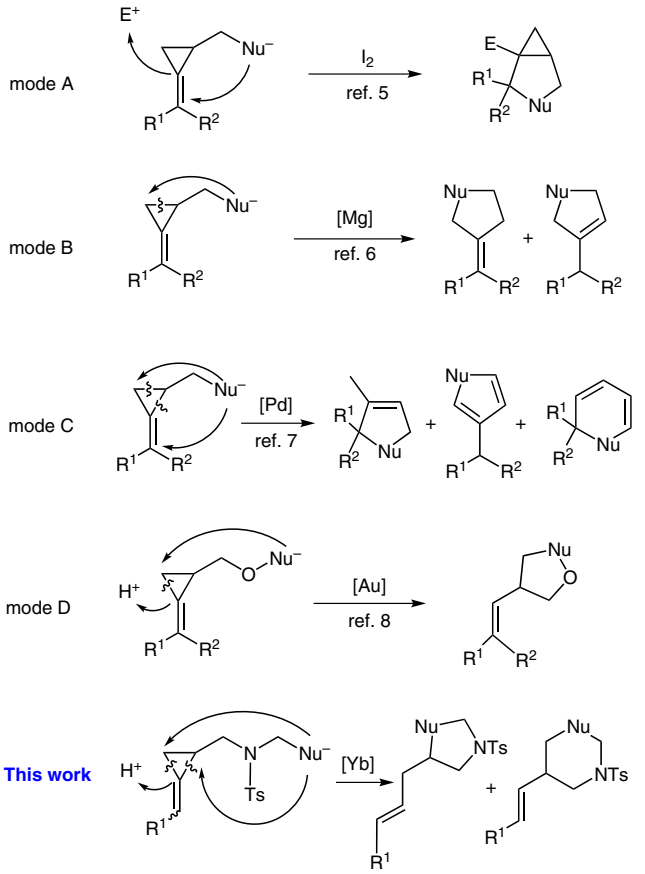


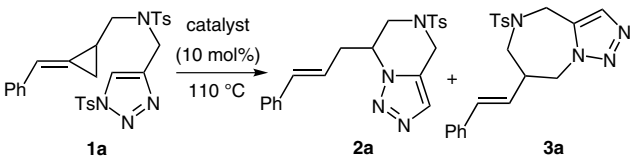
Scheme 1 Intramolecular nucleophilic addition of 2-substituted MCP. Nu = nucleophile. E = electrophile.

in a sealed reaction tube under strictly anhydrous conditions (Table 1, entry 25).

With the optimal reaction conditions in hand, we subsequently explored the substrate scope and the results are shown in Table 2. We found that the substituents on the aromatic rings of the MCP moiety slightly affected the reaction outcomes since only in the case of substrate **1f** in which the benzene ring of MCP-triazole has an electron-donating methoxyl group, the corresponding products **2f** and **3f** were obtained in 55% yield and others were all over 60% yield (Table 2, entries 3–11). Furthermore, the olefin configuration of MCP **1** did not have significant impact on the reaction outcomes. For example, MCP-triazoles **1a** and **1b** as well as **1g** and **1h** gave the similar results under the standard conditions (Table 2, entries 1, 2 and 7, 8). MCP-triazole **1l** with a heteroaromatic ring was also suitable in this reaction, but affording the corresponding products **2l** and **3l** in moderate yields, perhaps due to the coordination between the heteroatom with Lewis acid catalyst (Table 2, entry 12). All these cyclized products **2** and **3** can be easily separated by preparative thin layer chromatography (TLC).

It should be noted that using MCP-triazole **1m** as the substrate, in which the aromatic ring in the MCP moiety having an electron-withdrawing nitro group, none of the desired product was isolated and we only identified the formation of hydrolyzed product **4m** in 34% yield (Scheme 2). This result suggests that this reaction might be initiated from the coordination between the double

Table 1 Optimization of Reaction Conditions

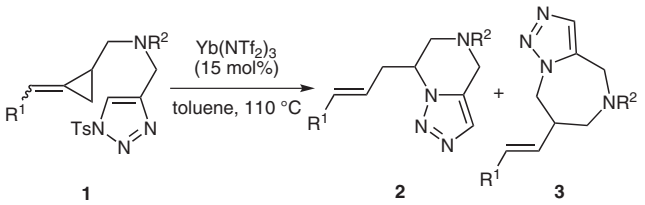


1a **2a** **3a**

Entry[a]	Catalyst	Solvent	Time (h)	**2a**/**3a**[b]	Yield (%)[c]
1	$BF_3{\cdot}OEt_2$	toluene	35	1:1.1	38
2	$Ti(O\textit{i}\text{-}Pr)_4$	toluene	>48	–	complex
3	$FeCl_2$	toluene	>48	–	complex
4	$FeCl_3$	toluene	>48	–	complex
5	HOTf	toluene	24	–	complex
6	AgOTf	toluene	35	1.2:1	45
7	$Cu(OTf)_3$	toluene	30	1:1	51
8	$Yb(OTf)_3$	toluene	30	1:1	64
9	$Bi(OTf)_3$	toluene	35	1:1.3	41
10	$Eu(OTf)_3$	toluene	35	1.1:1	63
11	$La(OTf)_3$	toluene	35	1:1	36
12	$Dy(OTf)_3$	toluene	30	1.3:1	58
13	$Tm(OTf)_3$	toluene	30	1.3:1	58
14	$Ce(OTf)_3$	toluene	46	1:1	50
15	$Ce(OTf)_4$	toluene	46	1:1.3	53
16	$In(OTf)_3$	toluene	35	1:1	82
17	$In(NTf_2)_3$	toluene	22	1:1	86
18	$Yb(NTf_2)_3$	toluene	25	1:1	88
19	$Yb(NTf_2)_3$	DCE	35	1.1:1	49[d]
20	$Yb(NTf_2)_3$	THF	>48	–	complex[d]
21	$Yb(NTf_2)_3$	hexane	35	1:1	36[d]
22	$Yb(NTf_2)_3$	MeCN	12	1:1	82[d]
23	$Yb(NTf_2)_3$	toluene	12	1:1	89[e]
24	$Yb(NTf_2)_3$	toluene	>48	–	complex[e,f]
25	$Yb(NTf_2)_3$	toluene	12	–	n.d.[e,g]

[a] Reaction conditions: **1a** (0.1 mmol), catalyst (0.01 mmol), toluene (2 mL), 110 °C.
[b] Compounds **2** and **3** can be separated individually by TLC.
[c] Isolated yield.
[d] Reaction was carried within a sealed tube.
[e] Conditions: 0.015 mmol (15 mol%) catalyst was added.
[f] Reaction was carried at 80 °C.
[g] The reaction was carried out under strictly anhydrous conditions; n.d. = not determined.

Table 2 $Yb(NTf_2)_3$-Catalyzed Ring-Opening Reaction of Triazole-Substituted MCP

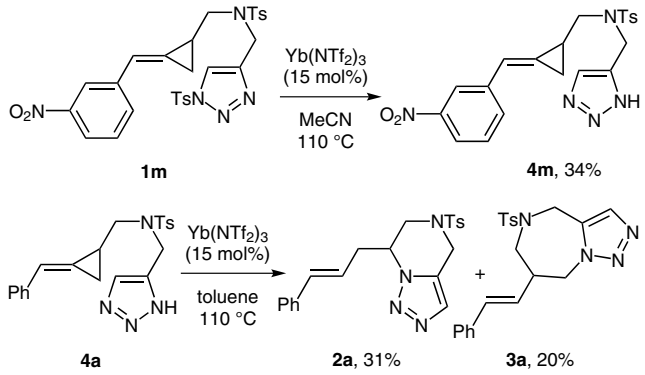


1 2 3

Entry[a]	Substrate	R^1	R^2	Config. **2**/**3**[b]		Yield (%)[c]
1	**1a**	Ph	Ts	*E*	1:1	89
2	**1b**	Ph	Ts	*Z*	1:1	72
3	**1c**	2-MeC_6H_4	Ts	*E*	1:1.6	71
4	**1d**	3-MeC_6H_4	Ts	*E*	1:1.7	79
5	**1e**	4-MeC_6H_4	Ts	*E*	1:1.9	64
6	**1f**	4-$MeOC_6H_4$	Ts	*Z*	1:1.3	55
7	**1g**	4-BrC_6H_4	Ts	*E*	1.4:1	76
8	**1h**	4-BrC_6H_4	Ts	*Z*	1.1:1	62
9	**1i**	4-BrC_6H_4	Bs	*E*	1:1	82
10	**1k**	4-ClC_6H_4	Ts	*E*	1:1.5	58
11	**1k**	1-Np	Ts	*E*	1:1.2	74
12	**1l**	2-thienyl	Ts	*Z*	1.2:1	33

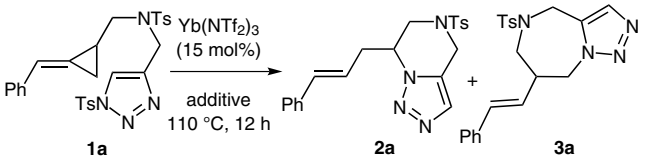
[a] Reaction conditions: **1a** (0.1 mmol), catalyst (0.01 mmol), toluene (2 mL), 110 °C.
[b] Compounds **2** and **3** can be separated individually by TLC.
[c] Isolated yield.

bond in the MCP moiety and the Lewis acid (π-activation).[10] The lower electron density in the double bond of substrate **1m** did not facilitate the intramolecular cyclization to take place. To verify this hypothesis, we synthesized relatively electron-rich substrate **4a** and examined its reactivity under the standard conditions. To our delight, the corresponding products **2a** and **3a** were obtained in 31% and 20% yields, respectively, indicating that compound **4** might be the reaction intermediate (Scheme 2).



Scheme 2 Mechanistic studies and control experiment

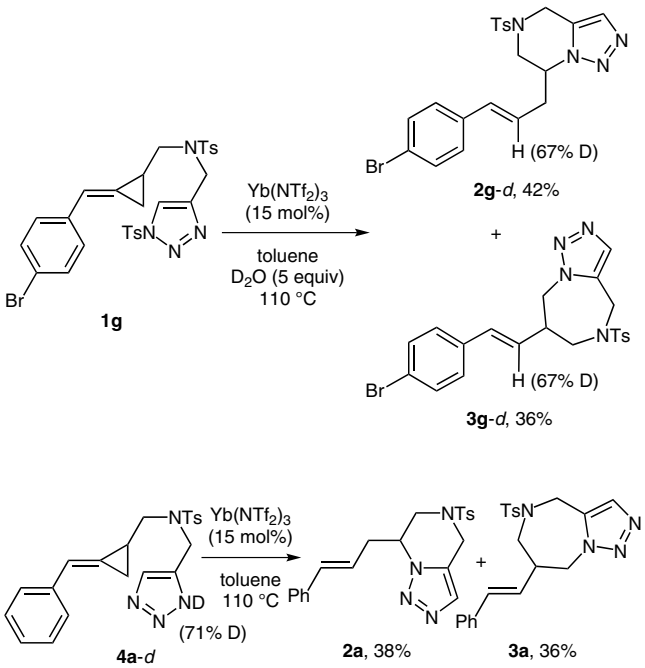
To identify whether this reaction proceeds through a SET process, several control experiments were conducted (Scheme 3). Addition of the electron-transfer scavenger 1,4-dinitrobenzene (0.2 equiv)[11] or the radical inhibitor hydroquinone (0.2 equiv) to the standard reaction mixtures did not impair the reaction outcomes, rendering that a SET reaction pathway may not be involved in the catalytic cycle.



additive	yield (%) (**2a** + **3a**)
none	89
1,4-dinitrobenzene	86
hydroquinone	85

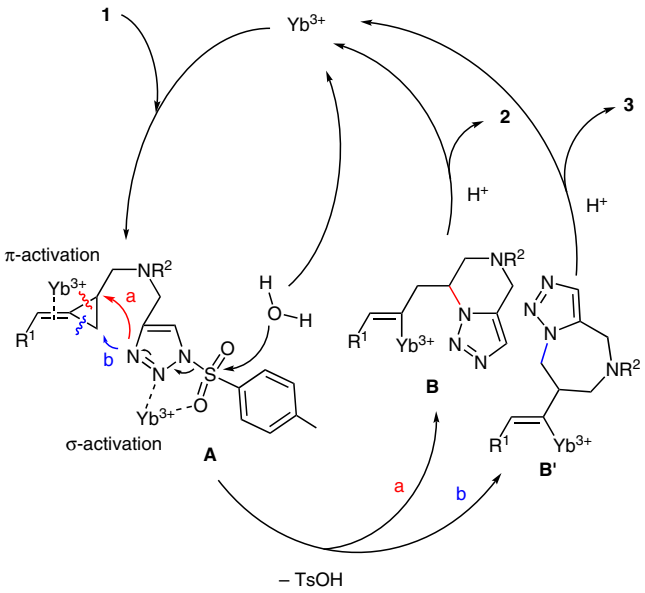
Scheme 3 Control experiments

To further verify the reaction pathway, the deuterium-labeling experiment was carried out by performing the reaction of **1g** in the presence of D_2O (5.0 equiv) under the standard conditions (Scheme 4). The deuterium-incorporated products **2g** and **3g** were formed in 42% and 36% yields along with 67% deuterium incorporation, respectively. This result suggests that ambient water is involved in the reaction. In addition, the deuterium-labeled substrate **4a**-*d* did not furnish any deuterium-incorporated products **2a** and **3a** under the standard conditions, indicating that an intramolecular hydrogen-transfer pathway is not involved in the reaction and the proton is derived from the ambient water source (Scheme 4).



Scheme 4 Isotopic labeling experiments

A proposed mechanism for this reaction is outlined in Scheme 5 on the basis of the above deuterium-labeling and control experiments. The Lewis acid first coordinates to the Ts-triazole moiety through a σ-activation[12] and the alkene moiety in the MCP part via a π-activation to give intermediate **A**, which may then undergo an intramolecular cyclization via two possible reaction pathways along with the hydrolysis of the sulfonyl group by ambient water to give the intermediates **B** (path a) and **B′** (path b). Protonation of the intermediates **B** and **B′** furnishes the corresponding 4*H*-[1,2,3]triazolo[1,5-*a*]pyrazine derivative **2** and 4*H*-[1,2,3]triazolo[1,5-*a*][1,4]diazepine **3** and regenerates the Yb^{3+} catalyst.



Scheme 5 A proposed reaction mechanism

In conclusion, we have developed a novel $Yb(NTf_2)_3$-catalyzed intramolecular cyclization of MCP-triazoles upon heating in toluene, affording triazole-containing six and seven-membered heterocycles in good yields. The reaction mechanism has been also proposed on the basis of control and deuterium-labeling experiments, indicating that the Lewis acid related π- and σ-activation plays an important role in this reaction. Efforts are under way to utilize this synthetic method to prepare biologically active substances.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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