

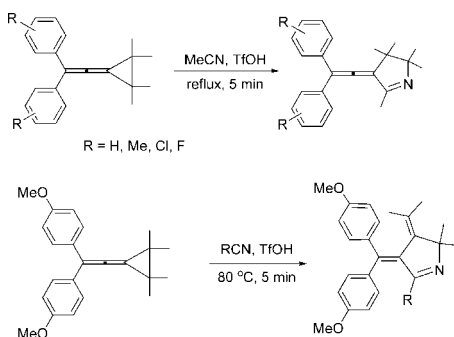
Brønsted Acid TfOH-Mediated [3 + 2] Cycloaddition Reactions of Diarylvinyldenecyclopropanes with Nitriles

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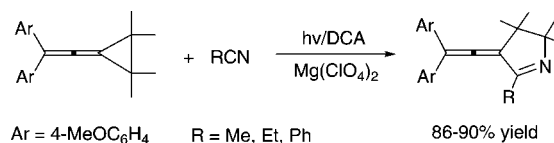


Diarylvinyldenecyclopropanes undergo a [3 + 2] cycloaddition reaction with MeCN in the presence of Brønsted acid TfOH to give the corresponding 3,4-dihydro-2H-pyrrole derivatives **2** in moderate to excellent yields under reflux within a short time. As for the diarylvinyldenecyclopropane substrate containing a strongly electron-donating methoxy group on the benzene ring, the reaction leads to the formation of a different type of 3,4-dihydro-2H-pyrrole derivatives **4** under the same conditions.

Introduction

Cycloaddition reactions of compounds containing highly strained cyclopropane ring moieties with nitriles have been the focus of organic synthesis for more than two decades.¹ Generally, these cycloadditions can proceed quickly upon photoirradiation^{1a-c} or by the treatment with strong Lewis or Brønsted acids^{1d-g} along with the release of ring strain. Diarylvinyldenecyclopropanes (VDCPs) **1** are one of the most remarkable organic compounds known since they have an allene moiety connected by a cyclopropane ring, and yet they are thermally stable and reactive substances. Many pioneering studies have been done involving mechanistic, theoretical, spectroscopic, and synthetic studies.^{1b,2,3} For example, Mizuno and co-workers have reported a [3 + 2] photocycloaddition of diarylvinyldenecyclopropanes with organic carbonitriles via photoinduced electron transfer in the presence of Mg(ClO₄)₂ and 9,10-dicyanoanthracene (DCA) (Scheme 1).^{1b} This interesting *excited state* reaction is fairly effective for the construction of 3,4-dihydro-2H-pyrrole derivatives containing an allene

SCHEME 1. [3 + 2] Photocycloaddition of Diarylvinyldenecyclopropanes with Nitriles via Photoinduced Electron Transfer



moiety, although it is only suitable for the diarylvinyldenecyclopropanes containing a methoxy group on the benzene ring.

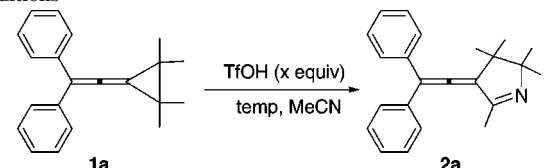
In this paper, we wish to report the Brønsted acid TfOH-mediated *ground state* cycloaddition of a variety of diarylvinyldenecyclopropanes (VDCPs) **1** with nitriles to give the corresponding 3,4-dihydro-2H-pyrrole derivatives **2** or **4** in good to excellent yields under mild conditions.

Results and Discussion

Initial examination was performed using diphenylvinyldenecyclopropane **1a** as the substrate in the presence of trifluoromethanesulfonic acid CF₃SO₃H (TfOH) (pK_a = 4.2 in acetic acid at 20 °C)⁴ in MeCN to develop the optimal conditions, and the results of these experiments are summarized in Table 1. We found that the corresponding 3,4-dihydro-2H-pyrrole derivative **2a** was pro-

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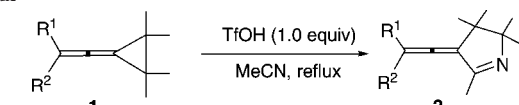
TABLE 1. Brønsted Acid TfOH-Mediated [3 + 2] Cycloaddition of Diphenylvinylidenecyclopropane **1a** with MeCN under Various Conditions


entry ^a	x	temp/°C	time/min	yield of 2a ^b /%
1	1.0	rt	15	49
2	1.5	rt	15	55
3	1.0	50	15	90
4	1.5	50	5	93
5 ^c	0.5	50	60	54
6	1.5	reflux	5	91
7	1.0	reflux	5	93
8 ^d	0.5	reflux	390	67

^a Reaction conditions: VDCP (0.18 mmol) was dissolved in dry MeCN (2 mL) under argon atmosphere. TfOH (x equiv) was added, and then the mixture was stirred at different temperatures for different times. ^b Isolated yield. ^c 40% of **1a** was recovered. ^d 32% of **1a** was recovered.

duced under various conditions in MeCN in moderate to high yields. For example, using 1.0 and 1.5 equiv of TfOH as a promoter at room temperature (20 °C), the reaction proceeded smoothly to give **2a** in 49 and 55% yield within 15 min, respectively (Table 1, entries 1 and 2). Increasing the reaction temperature to 50 °C accelerated the reaction rate, affording **2a** in 90% yield within 15 min with 1.0 equiv of TfOH and in 93% yield within 5 min with 1.5 equiv of TfOH (Table 1, entries 3 and 4). In the presence of 0.5 equiv of TfOH, the reaction became sluggish to produce **2a** in 54% yield along with the recovery of 40% of **1a** even after extending the reaction time to 60 min (Table 1, entry 5). Under reflux in MeCN, **2a** was produced in 91 and 93% yield in the presence of 1.5 and 1.0 equiv of TfOH within 5 min, respectively (Table 1, entries 6 and 7). When using 0.5 equiv of TfOH as a promoter under reflux in MeCN, **2a** was formed in 67% by extending the reaction time to 390 min (Table 1, entry 8). These results indicated that the best reaction conditions are to carry out the reaction in MeCN under reflux in the presence of 1.0 equiv of TfOH.

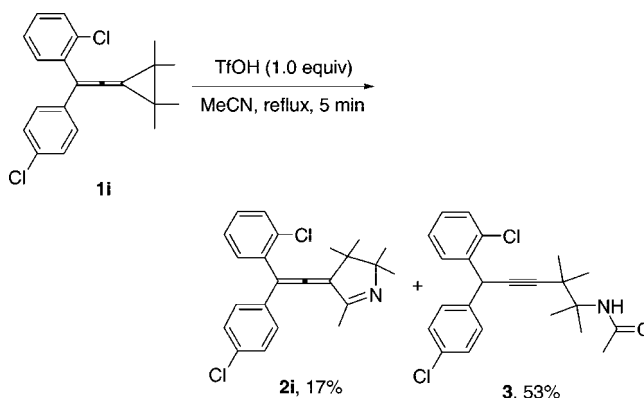
With these optimized reaction conditions identified, we next examined the cycloaddition of a variety of diarylvinyldienecyclopropanes **1** with MeCN. The results are shown in Table 2. As for symmetrical diarylvinyldienecyclopropane **1b** and unsymmetrical diarylvinyldienecyclopropanes **1e**, **1f**, and **1h**

TABLE 2. Brønsted Acid TfOH-Mediated [3 + 2] Cycloaddition of a Variety of Diarylvinyldienecyclopropanes **1** with MeCN under Reflux


entry ^a	R ¹ /R ²	time/min	yield of 2 ^b /%
1	<i>p</i> -MeC ₆ H ₄ / <i>p</i> -MeC ₆ H ₄ 1b	5	2b , 90
2	<i>p</i> -FC ₆ H ₄ / <i>p</i> -FC ₆ H ₄ 1c	5	2c , 71
3	<i>p</i> -ClC ₆ H ₄ / <i>p</i> -ClC ₆ H ₄ 1d	5	2d , 70
4	<i>p</i> -MeC ₆ H ₄ / <i>p</i> -C ₆ H ₅ 1e	5	2e , 90
5	<i>m</i> , <i>p</i> -di-Me ₂ C ₆ H ₃ /C ₆ H ₅ 1f	5	2f , 94
6	<i>p</i> -ClC ₆ H ₄ /C ₆ H ₅ 1g	5	2g , 75
7	<i>o</i> -MeC ₆ H ₄ /MeC ₆ H ₄ 1h	5	2h , 56
8 ^c	<i>p</i> -ClC ₆ H ₄ / <i>o</i> -ClC ₆ H ₄ 1i	10	2i , 17

^a Reaction conditions: VDCP (0.18 mmol) was dissolved in dry MeCN under argon atmosphere, TfOH (1.0 equiv) was added, and then the reaction mixture was refluxed for 5 min. ^b Isolated yield. ^c See Scheme 2.

SCHEME 2. Unexpected Reaction of Diarylvinyldienecyclopropane **1i** with MeCN Promoted by TfOH

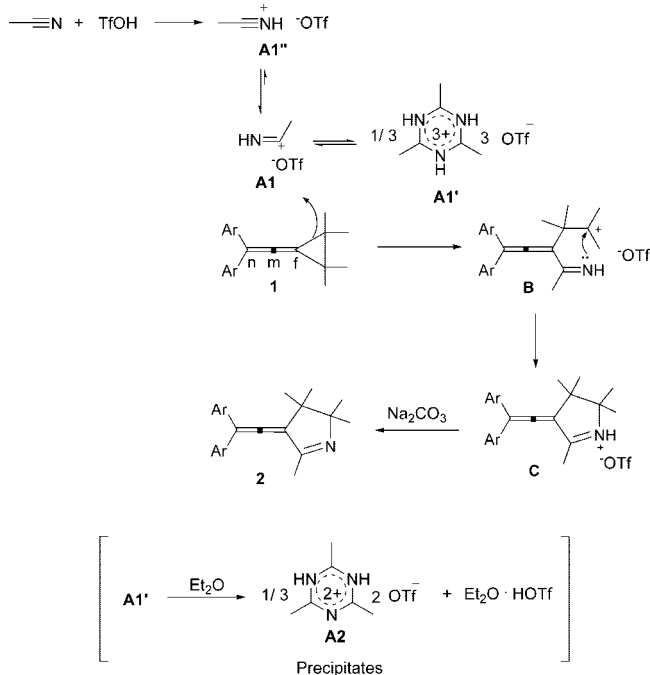


having a moderately electron-donating methyl group on the benzene ring, the corresponding 3,4-dihydro-2*H*-pyrrole derivatives **2b**, **2e**, **2f**, and **2h** were obtained in high yields (Table 2, entries 1, 4, 5, and 7). Adding a moderately electron-withdrawing chloro or fluoro atom on the benzene ring of symmetrical diarylvinyldienecyclopropanes **1c** and **1d** as well as unsymmetrical diarylvinyldienecyclopropane **1g** afforded the corresponding 3,4-dihydro-2*H*-pyrrole derivatives **2c**, **2d**, and **2g** in moderate yields (Table 2, entries 2, 3, and 6). Interestingly, when using unsymmetrical diarylvinyldienecyclopropane **1i** bearing an *ortho*-chloro atom on the benzene ring as the substrate, the yield of the expected product **2i** was only 17% (Table 2, entry 8) along with another unexpected product **3** in 53% yield, which is derived from a Ritter reaction process (Scheme 2).^{1g,5}

A plausible mechanism for this Brønsted acid TfOH-mediated [3 + 2] cycloaddition of diarylvinyldienecyclopropane **1** with

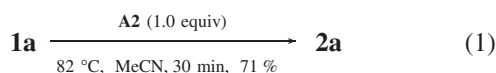
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SCHEME 3. Proposed Mechanism for the [3 + 2] Cycloaddition Reaction


MeCN is shown in Scheme 3. First, there is an equilibrium between intermediates **A1**, **A1'**, and **A1''** in the reaction of acetonitrile and TfOH according to previous literature.^{6a,b} Intermediate **A1** undergoes an electrophilic attack to the far position of allene moiety from the aryl groups (noted as f) of diarylvinylidenecyclopropane **1** to afford the corresponding cyclopropane ring-opened cationic intermediate **B**, which undergoes the subsequent intramolecular cyclization reaction to give cationic intermediate **C**. Treatment of **C** with Na_2CO_3 furnishes 3,4-dihydro-2H-pyrrole derivative **2** (Scheme 3). This proposed mechanism could explain why 1 equiv or more of TfOH is required in above reaction to produce **2** in good yield.

To further clarify the reaction mechanism, we conducted the addition of 0.18 mmol of TfOH to 2.0 mL of MeCN under reflux for 15 min followed by removal of the solvent in vacuo. The IR spectrum of the residue did not contain an absorption band at 2245 cm^{-1} [$\nu(\text{CN})$ of nitrile]^{6a} but gave a weakly broad absorption band at 2500 cm^{-1} and two strong absorption bands at 3327 and 3210 cm^{-1} , respectively,^{6b} suggesting the existence of intermediates **A1** and **A1'** as shown in Scheme 3.⁶ Adding Et_2O to the residue afforded many white precipitates which could be recrystallized from MeOH/ Et_2O to give intermediate **A2** as shown in Scheme 3 as well by comparing its IR spectrum with the literature value.^{6b} The resulting precipitates could also promote the cycloaddition of **1a** with MeCN (as a solvent) to provide **2a** in moderate yield, although a prolonged reaction time is required (eq 1). All of these facts indicated that the intermediates **A1** and **A1'** are active species in this reaction.



As to the Ritter reaction product **3** in the reaction of diarylvinylidenecyclopropane **1i** with MeCN, a plausible mechanism is shown in Scheme 4. Instead of Brønsted acid TfOH being captured by MeCN, **1i** is first protonated by TfOH at the near position of the allene moiety from the aryl groups (noted as n) along with the cyclopropane ring opening to give the

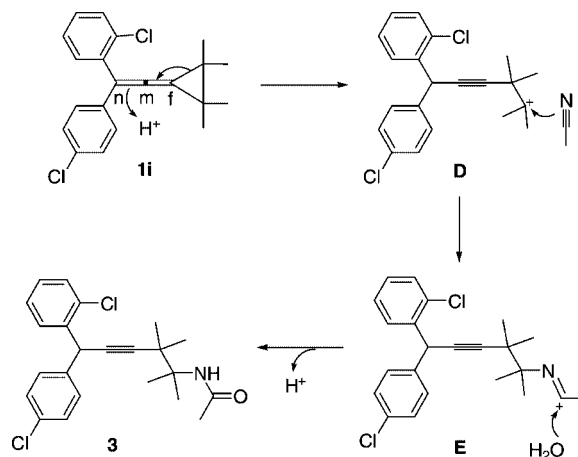
SCHEME 4. Proposed Mechanism for the Ritter Reaction of 1i with MeCN


TABLE 3. Brønsted Acid TfOH-Promoted [3 + 2] Cycloaddition of Diphenylvinylidenecyclopropane 1j with Nitriles

entry ^a	RCN	yield of 4 ^b /%
1	MeCN	4a , 94
2	ⁿ PrCN	4b , 75
3	PhCH ₂ CN	4c , 58
4	PhCN	4d , 64
5	CH ₂ =CHCN	4e , 72

^a Reaction conditions: VDPC (0.1 mmol) was dissolved in dry RCN (2 mL) under argon atmosphere, TfOH (1.0 equiv) was added, and then the reaction mixture was refluxed for 5 min. ^b Isolated yield.

corresponding cationic intermediate **D**.⁷ Intermediate **D** is captured by MeCN to give the cationic intermediate **E**, which is hydrolyzed by water to furnish the product **3** (Scheme 4). Electron-deficient diarylvinylidenecyclopropane **1i** and the *ortho*-chloro group on the benzene ring can sterically and electronically retard the reaction with cationic intermediate **A**. Therefore, proton-induced intramolecular rearrangement takes place preferentially to give cationic intermediates **D** and **E** as well as the subsequent Ritter reaction product **3**.

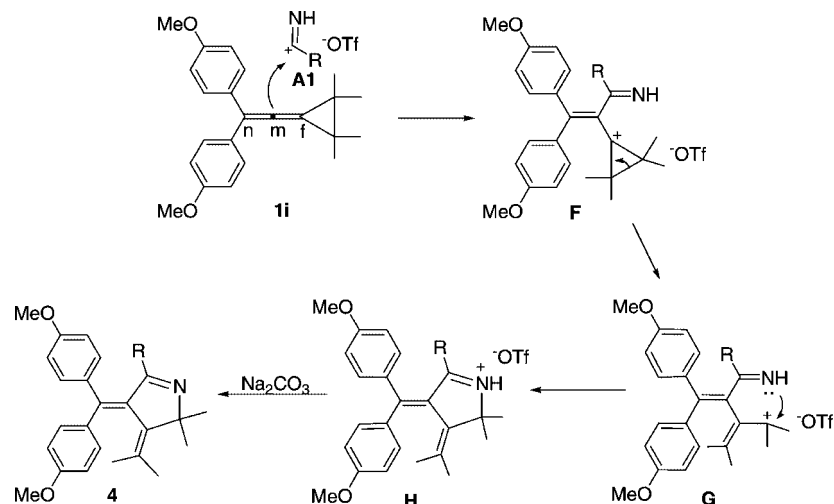
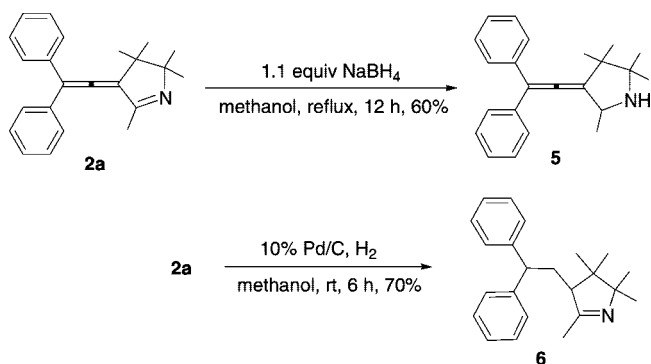
Moreover, using di(4-methoxyphenyl)vinylidenecyclopropane **1j** as the substrate to react with MeCN in the presence of 1.0 equiv of TfOH under reflux,⁸ we found that 3,4-dihydro-2H-

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SCHEME 5. Proposed Mechanism for the [3 + 2] Cycloaddition Reaction of **1j** with NitrilesSCHEME 6. Reduction of **2a** with NaBH_4 and Pd/H_2 in Methanol

pyrrole derivative **4a** with an isopropylidene group on the five-membered ring was formed in 94% yield rather than the “normal” product containing an allene moiety such as **2a–2i** (Table 3, entry 1). In addition, **1j** can react smoothly with various nitriles to give the corresponding 3,4-dihydro-2H-pyrrole derivatives as **4b**, **4c**, **4d**, and **4e** in good yields (Table 3, entries 2–5). This interesting different reaction capability with nitriles may be due to the strongly electron-donating methoxy groups on the benzene rings of **1j**.

A plausible mechanism for the [3 + 2] cycloaddition reaction of **1j** with nitriles mediated by TfOH is shown in Scheme 5. As in Scheme 3, RCN is first protonated by Brønsted acid TfOH to give the corresponding cationic intermediate **A1**.⁶ Intermediate **A1** undergoes an electrophilic attack to the middle position of allene moiety (noted as m) of **1j** to give the corresponding intermediate **F**, which immediately undergoes a ring-opening process to afford cationic intermediate **G**. Intramolecular cyclization takes place to give cationic intermediate **H**, which furnishes the corresponding product **4** through neutralization with Na_2CO_3 (Scheme 5). The strongly electron-donating methoxy groups on the benzene rings of **1j** increases the electron density at the middle position of the allene moiety, facilitating the electrophilic attack of cationic intermediate **A**. Therefore, the reaction takes place in a different pathway.

The cycloaddition product **2a** of **1a** with MeCN could be converted to the corresponding pyrrolidine **5** in 60% yield by reduction with NaBH_4 in methanol (Scheme 6).^{1b} Moreover, with 10% Pd/C in methanol under hydrogen gas atmosphere, **2a** was transformed to the corresponding 3,4-dihydro-2H-pyrrole **6** in 70% yield (Scheme 6).⁹

In conclusion, we disclosed a [3 + 2] cycloaddition reaction using VDCPs **1** with nitriles promoted by Brønsted acid TfOH in this paper. In this transformation, the corresponding 3,4-dihydro-2H-pyrrole derivatives **2** or **4** can be obtained in moderate to excellent yields under mild conditions within short reaction time. A considerable range of aromatic group substituted VDCPs **1** has been examined in the reaction. These processes provide an efficient route to the synthesis of different 3,4-dihydro-2H-pyrrole derivatives according to different substrates. Moreover, pyrrolidine derivatives **5** and **6** were obtained in good yields by the further transformations of the cycloadduct **2a**. Efforts are underway to elucidate the mechanistic details and the scope and limitations of this reaction in the laboratory.

Experimental Section

General Procedure for the Cycloaddition of **1a–1h with MeCN.** Under an argon atmosphere, diarylvinylidenecyclopropane (VDCP) (0.18 mmol) was dissolved in MeCN (2.0 mL), and then the mixture was heated to the reflux temperature. To the resulting 18 μL solution of TfOH (1.0 equiv) was added, and reaction mixtures were stirred for 5–15 min. The reaction was quenched by addition of anhydrous Na_2CO_3 . After the solid was filtrated off, the solution was washed with CH_2Cl_2 ($2 \times 10 \text{ mL}$). The combined organic phases were concentrated in vacuo, and the residue was purified by a flash column chromatography on silica gel column with petroleum ether/EtOAc (3:1) as an eluent.

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Supporting Information Available: Detailed experimental procedures, ^1H and ^{13}C NMR spectra for the cycloadducts **2** and **4**, Ritter reaction product **3**, and the reduction products **5** and **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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