

The Lewis Acids Catalyzed Aza-Diels–Alder Reaction of Methylene cyclopropanes with Imines

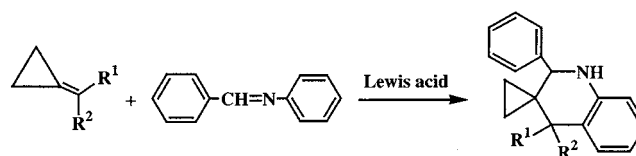
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ABSTRACT



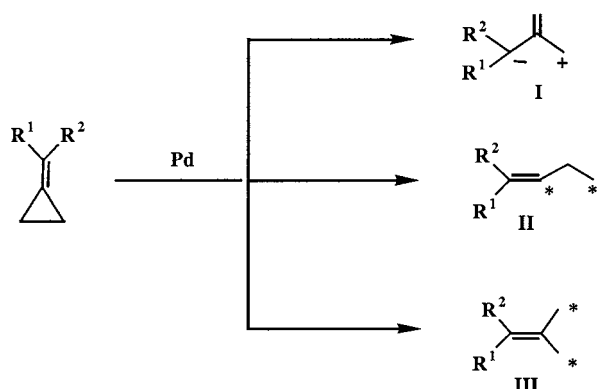
R¹ and R² could be aromatic or aliphatic group.

The methylenecyclopropanes can react with various imines to give the aza-Diels–Alder adducts in good yields in the presence of Lewis acids.

Methylene cyclopropanes (MCPs) are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.¹ MCPs undergo a variety of ring-opening reactions because the relief of ring strain provides a potent thermodynamic driving force. Three kinds of reaction patterns of MCPs have been disclosed (Scheme 1) for reactions with transition metals such as Pd, Rh, Ru, and Pt. MCPs can react with polar reactants such as

ROH,² R₂NH,³ malonate derivatives,⁴ carbon dioxide,⁵ aldehydes,⁶ and imines⁷ in the presence of a Pd catalyst to give type I products. MCPs also can react with nonpolar reactants such as R₃SiH,⁸ R₃SnH,⁹ R₂B–BR₂,¹⁰ R₃Si–BR₂,¹¹ R₃Si–CN,¹² and olefins¹³ in the presence of a Pd, Ru, or Rh metal

Scheme 1. Three Reaction Patterns of MCPs



(1) For a recent review see: Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *2*, 111. For synthesis of MCPs see: Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 598.

(2) (a) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3365. (b) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270.

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(11) Sugimoto, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015.

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catalyst to afford the type II and/or type III products depending on the reaction conditions (Scheme 1).

Recently, we reported that the ring-opening reaction of MCPs took place via another novel procedure to give the corresponding ring-opened products under mild conditions in the presence of Lewis acids.¹⁴ This interesting result stimulated us to further investigate Lewis acid-catalyzed reactions of MCPs with other reactants. Herein we wish to report an unprecedented Lewis acid-catalyzed aza-Diels–Alder reaction of MCPs with imines under more mild conditions in which the cyclopropyl rings of MCPs remain unopened.¹⁵

With use of di(4-methoxyphenyl)methylenecyclopropane (**1a**) as a substrate, the reaction of **1a** with imine **2a** has been carefully examined in the presence of various Lewis acids or Bronsted acids (Table 1). We found that the reactions

Table 1. The Effects of Various Lewis Acids (0.025 mmol) or Bronsted Acids in the Reactions of MCP (**1a**, 0.25 mmol) with Imine **2a** (0.25 mmol)

1a: R = *p*-MeOC₆H₄

entry	Lewis acid	yield/% ^a (time/h)
1	none	no reaction
2	Yb(OTf) ₃	100 (9 h)
3	Sc(OTf) ₃	100 (5 h)
4	Sn(OTf) ₃	100 (8 h)
5	Zr(OTf) ₃	96 (12 h)
6	Cu(OTf) ₃	94 (12 h)
7	Zn(OTf) ₃	88 (12 h)
8	BF ₃ ·OEt ₂	92 (23 h)
9	CF ₃ SO ₃ H	99 (22 h)
10	C ₈ F ₁₇ SO ₃ H	96 (22 h)

^a Isolated yields.

proceeded smoothly in the presence of Lewis acids Sn(OTf)₂, Sc(OTf)₃, Yb(OTf)₃, Zr(OTf)₄, BF₃·Et₂O, Zn(OTf)₂, or Cu(OTf)₂ (10 mol %) to give the corresponding aza-Diels–Alder reaction product **3a** in high yields at room temperature (20 °C) (Table 1, entries 2–8). Yb(OTf)₃, Sc(OTf)₃, and Sn(OTf)₂ are the best Lewis acids in this reaction to give **3a** in quantitative yields (100%) within 10 h in 1,2-dichloroethane

(13) The reaction of reactions of MCPs with unsaturated carbon bonds had been extensively studied; please see the following review: Laurens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(14) (a) The Lewis acid-catalyzed ring-opening reactions of MCPs: Shi, M.; Xu, B. *Org. Lett.*, **2002**, *4*, 2145 and references therein. (b) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Tetrahedron Lett.* **2002**, *43*, 8019.

(15) The papers related aza-Diels–Alder reactions of dienophiles (cyclopentadienes, vinyl sulfides, or vinyl ethers) with imines. Please see: (a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195. (b) Yadav, J. S.; Reddy, B. V. S.; Madhuri, C. R.; Sabitha, G. *Synthesis* **2001**, 1065. (c) Nagarajan, R.; Perumal, P. T. *Synth. Commun.* **2001**, *31*, 1733. (d) Anniyappan, M.; Nagarajan, R.; Perumal, P. T. *Synth. Commun.* **2002**, *32*, 99.

(DCE) at room temperature (20 °C) (Table 1, entries 2–4). In addition, it should be emphasized here that Bronsted acid R₃SO₃H (CF₃SO₃H or C₈F₁₇SO₃H) also can catalyze this reaction under the same conditions, although the achieved yields are slightly lower than those of Sn(OTf)₂ and Sc(OTf)₃ (Table 1, entries 9 and 10). But no reaction occurred in the absence of catalyst (Table 1, entry 1). This result suggests that a Lewis acid or a Bronsted acid catalyst plays a critical role in this reaction.

The structure of **3a** was established by the ¹H and ¹³C NMR spectroscopic data (Supporting Information) and X-ray analysis. The X-ray crystal structure of **3a** is shown in Figure 1.¹⁶

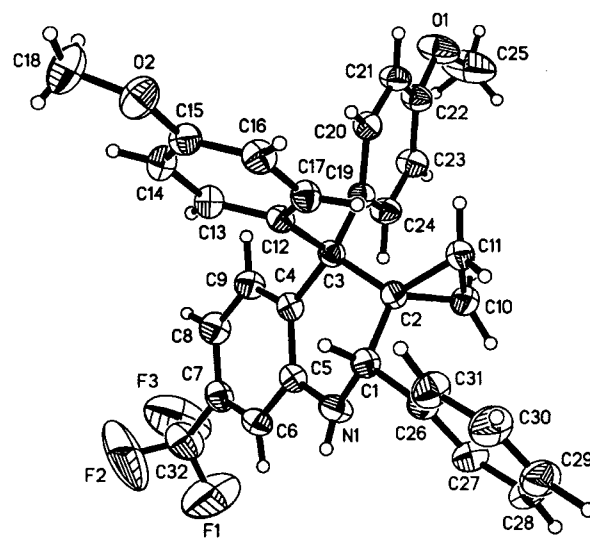


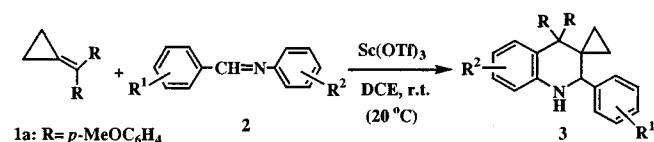
Figure 1. The X-ray crystal structure of **3a**.

Then, we carried out this interesting aza-Diels–Alder reaction of MCP **1a** with various imines in the presence of Sc(OTf)₃ (10 mol %) under the optimized conditions. The results were summarized in Table 2. In most cases, the corresponding aza-Diels–Alder products **3** were obtained in excellent yields (Table 2, entries 2–6). The electron-donating or electron-withdrawing substituents (R¹ and R²) on the phenyl ring did not significantly affect this reaction. Only for imine **2b**, having a substituent on the ortho-position of the aromatic amine (R² = *o*-MeO–), was the reaction sluggish, and the product was obtained in a trace amount due to the steric hindrance of imine **2b** (Table 2, entry 1).

Using diphenylmethylenecyclopropane (**1b**), di(*p*-methoxyphenyl)methylenecyclopropane (**1c**), and di(*p*-chlorophe-

(16) The X-ray data of **3a** have been deposited as CCDC number 198190. Empirical formula: C₃₂H₂₈F₃NO₂. Formula weight: 515.55. Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.20 × 0.20 × 0.30 mm. Crystal system: orthorhombic. Lattice type: primitive. Lattice parameters: *a* = 17.406(2) Å, *b* = 13.9744(18) Å, *c* = 22.076(3) Å, α = 90°, β = 90°, γ = 90°, *V* = 5369.7(12) Å³. Space group: *Pbca*. *Z* value = 8. *D*_{calc} = 1.275 g/cm³. *F*₀₀₀ = 2160. μ(Mo Kα) = 1.98 cm⁻¹. Diffractometer: Rigaku AFC7R. Residuals: *R* = 0.0629, *R*_w = 0.1508.

Table 2. The Aza-Diels–Alder Reactions of MCP **1a** (0.25 mmol) with Various Imines (0.25 mmol) in the Presence of Lewis Acid Sc(OTf)₃ (0.025 mmol)



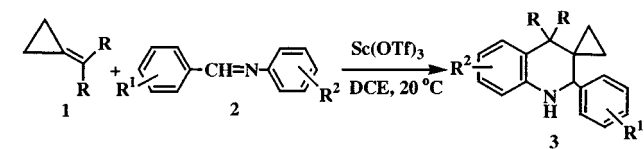
b: R¹ = H, R² = *o*-MeO; c: R¹ = H, R² = *p*-Cl; d: R¹ = H, R² = *p*-EtO;
e: R¹ = *p*-MeO, R² = H; f: R¹ = *p*-NO₂, R² = H; g: R¹ = H, R² = H.

entry ^a	R ¹	R ²	yield/% ^b
1	H	<i>o</i> -MeO	3b , trace
2	<i>p</i> -Cl	H	3c , 100
3	H	<i>p</i> -EtO	3d , 100
4	<i>p</i> -MeO	H	3e , 100
5	<i>p</i> -NO ₂	H	3f , 82
6	H	H	3g , 90

^a All reactions were carried out with MCP **1a** (0.25 mmol) and imines (0.25 mmol) in DCE at 20 °C for 24 h. ^b Isolated yields

nyl)methylenecyclopropane (**1d**) as substrates, we also examined their aza-Diels–Alder reactions under the same conditions. The results are elucidated in Table 3. The

Table 3. The Reactions of MCPs **1** with Imines **2** in the Presence of Sc(OTf)₃



entry ^a	substrate	R ¹	R ²	yield/% ^b
1	1b	H	<i>m</i> -CF ₃	3h , 65
2	1b	<i>p</i> -Cl	H	3i , 100
3	1b	H	H	3j , 82
4	1c	H	<i>m</i> -CF ₃	3k , 98
5	1c	H	<i>p</i> -EtO	3l , 79
6	1d	H	<i>m</i> -CF ₃	no reaction

^a All reactions were carried out with MCPs **1** (0.25 mmol) and imines (0.25 mmol) in DCE at 20 °C for 24 h. ^b Isolated yields.

substituents on the benzene ring of MCPs significantly affected the reaction. For **1d** having an electron-withdrawing group (Cl–) on the phenyl ring, no reaction occurred (Table 3, entry 6). For other substrates, the reactions proceeded very well and the addition products were obtained in good to very high yields (Table 3, entries 1–5). Their structures were also established by the ¹H and ¹³C NMR spectroscopic data (Supporting Information). In addition, we also selected one Diels–Alder product for X-ray analysis. The X-ray crystal structure of **3j** is elucidated in Figure 2.¹⁷

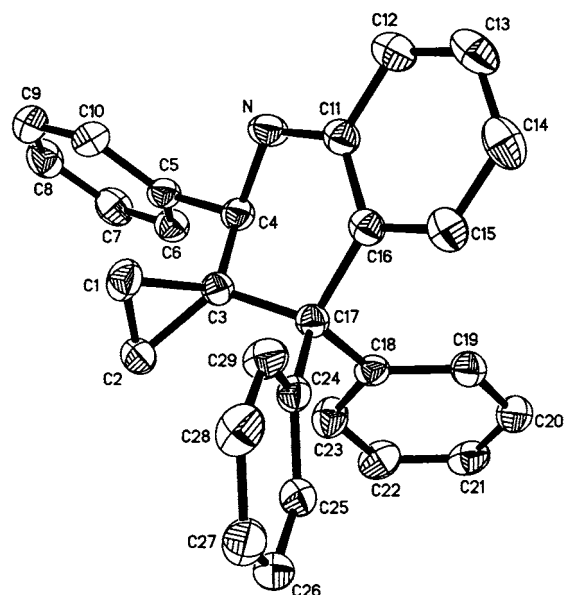
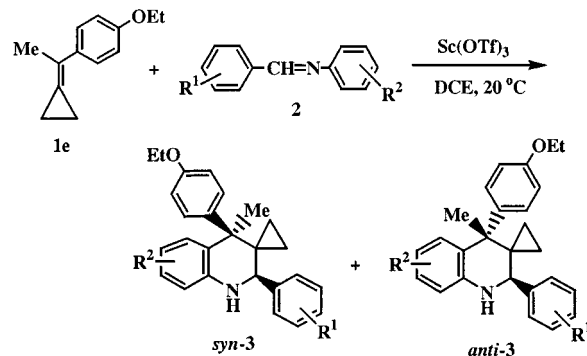


Figure 2. The X-ray crystal structure of **3j**.

On the other hand, we also examined the reactions of unsymmetric MCP **1e** (monoalkyl-substituted MCPs) with imines under the same conditions. The results are summarized in Table 4. We found that **1e** reacted with various

Table 4. The Reactions of Unsymmetric MCP **1e** with Imines in the Presence of Sc(OTf)₃



entry ^a	R ₁	R ₂	yield/% ^b (syn/anti)
1	H	<i>m</i> -CF ₃	3m , 94 (7/1)
2	H	<i>o</i> -MeO	3n , 86 (3/1)
3	H	<i>p</i> -EtO	3o , 75 (3/1)
4	<i>p</i> -MeO	H	3p , 90 (1.8/1)
5	<i>p</i> -NO ₂	H	3q , 79 (5/1)
6	H	H	3r , 100 (21/1)

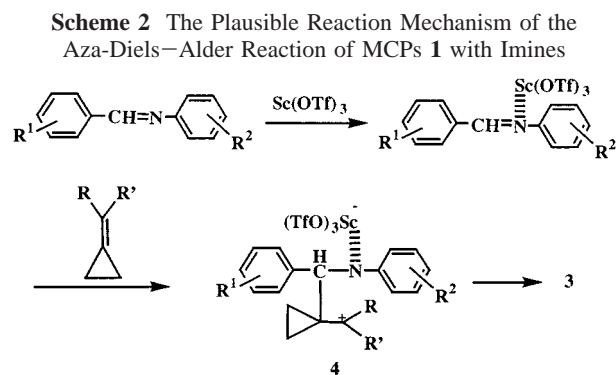
^a All reactions were carried out with MCP **1e** (0.25 mmol) and imines (0.25 mmol) in DCE at 20 °C for 24 h. ^b Isolated yields

imines very well to give the corresponding aza-Diels–Alder adducts in good to very high yields (Table 4, entries 1–6). Especially for imine **2b** having a substituent on the ortho-

position of the aromatic amine, the reaction also proceeded smoothly to afford the corresponding Diels–Alder adduct **3n** in good yield (Table 4, entry 2). We believe that this is because MCP **1e** has a small methyl group that reduces the steric hindrance of dienophile. Therefore, the aza-Diels–Alder reaction of **1e** with sterically hindered imine **2b** can take place as well. This result suggests that the steric effect also plays an important role in this type of aza-Diels–Alder reaction. The ratios of *syn*-**3** and *anti*-**3** were determined based on the ¹H NMR spectroscopic data (see the Supporting Information).¹⁸

It should be mentioned that for alkylimines and both alkyl-substituted MCPs, no reactions occurred.

An interesting finding in this paper is that in this reaction, the cyclopropyl rings of MCPs **1** remain unopened in the presence of Lewis acids. Thus, this reaction is another type of MCPs transformation catalyzed by Lewis acids. On the basis of the previous investigations of aza-Diels–Alder reactions of imines with 2-methoxypropene by Kobayashi,¹⁹ a plausible mechanism for this type of aza-Diels–Alder reaction of MCPs with imines is proposed in Scheme 2. The cyclopropylmethyl cation in intermediate **4** is further stabilized by two substituents on the double bond.²⁰ Thus, the intramolecular Friedel–Crafts reaction quickly takes place



to give the corresponding aza-Diels–Alder adducts **3** rather than the cyclopropylmethyl cation rearranged products.

In conclusion, we disclosed a previously unknown transformation process of MCPs by the reaction with imines in the presence of Lewis acid to give aza-Diels–Alder products **3** in good to excellent yields. A range of imines derived from aromatic amine and arylaldehydes have been examined. This process provides a novel and efficient route to the synthesis of quinoline derivatives. Efforts are in progress to elucidate the mechanistic details of this reaction and to determine its scope and limitations.

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Supporting Information Available: Spectroscopic data of the compounds (¹H and ¹³C NMR spectra data) shown in Tables 1–4 and a detailed description of experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) The X-ray data of **3j** have been deposited as CCDC number 188124. Empirical formula: C₂₉H₂₅N. Formula weight: 387.50. Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.20 × 0.20 × 0.30 mm. Crystal system: triclinic. Lattice type: primitive. Lattice parameters: *a* = 9.3293(8) Å, *b* = 9.8693(9) Å, *c* = 11.9147(11) Å, α = 88.580(2)°, β = 82.605(2)°, γ = 72.142(2)°, *V* = 1035.36(16) Å³. Space group: *P*1̄. *Z* value = 2. *D*_{calc} = 1.243 g/cm³. *F*₀₀₀ = 412. μ (Mo K α) = 1.98 cm⁻¹. Diffractometer: Rigaku AFC7R. Residuals: *R* = 0.0376, *R*_w = 0.0635.

(18) The stereoisomers of *syn*-**3** and *anti*-**3** were determined based on the chemical shift of ¹H NMR spectroscopic data. Please see: Primke, H.; Sarin, G. S.; Kohlstruk, S.; Adiwidjaja, G.; de Meijere, A. *Chem. Ber.* **1994**, *127*, 1051.

(19) Kobayashi has concluded that this type of aza-Diels–Alder reaction proceeds via a stepwise mechanism. Please see ref 16a.

(20) The rearrangement of cyclopropylmethyl cation has already been studied extensively. It is reasonable that the substituents on the double bond further stabilize the cation. Please see: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 5th ed.; Plenum Press: New York, 1998; pp 221 and 419.