Tetrahedron Letters 55 (2014) 3041–3044

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper(II)–acid catalyzed cyclopropanation of 1,3-dienamides by electrophilic activation of α-aryl diazoesters

Eiji Tayama *, Kouki Horikawa, Hajime Iwamoto, Eietsu Hasegawa

Department of Chemistry, Faculty of Science, Niigata University, Niigata 950-2181, Japan

A R T I C L E I N F O

Article history:
Received 24 February 2014
Revised 20 March 2014
Accepted 26 March 2014
Available online 3 April 2014

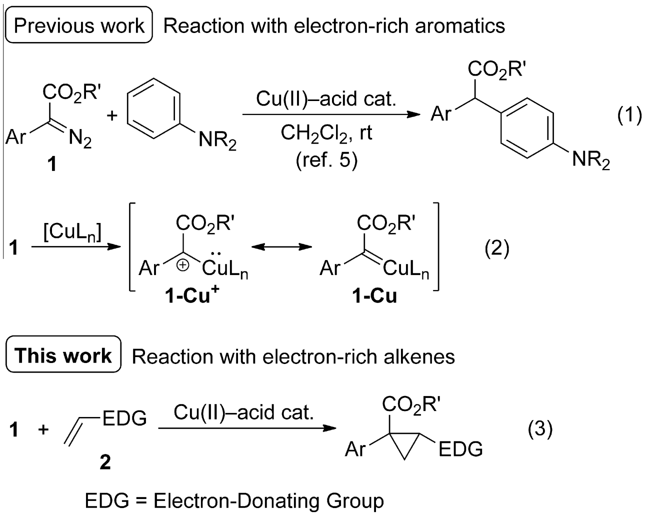
Keywords:
Cycloaddition
Diazo compound
Alkene
Diastereoselectivity
Regioselectivity

A B S T R A C T

Copper(II)–acid catalyzed cyclopropanation of electron-rich alkenes, such as 1,3-dienamides, with α-aryl diazoesters are described. The reaction could be performed without rare metal catalysts, excess substrate, or the need for the slow addition of the diazoesters.

The transition metal-catalyzed cyclopropanation of alkenes with α-diazoesters is a powerful and efficient synthetic method that enables the preparation of valuable building blocks for natural product synthesis.[1] There are several well-studied examples of the reaction catalyzed by Rh, Ru, and Cu(I) complexes; however, these reactions are of limited synthetic use due to the high cost of the catalysts, especially Rh and Ru complexes. Thus, it is important to develop inexpensive and convenient methods for synthetic organic chemists. Copper(I) complexes,[2,3] such as copper(I) triflate [Cu(OTf)·Ln] or tetrakis (acetonitrile) copper(I) hexafluorophosphate [$(MeCN)_4CuPF_6$], have the advantage of reduced cost, but their strong catalytic activity results in undesirable side reactions such as the dimerization of α-diazocarbonyl compounds.[1,4] To suppress the side reactions, the use of excess alkene or the slow addition of α-diazocarbonyl compounds must be considered. In contrast, copper(II) salts, such as copper(II) triflate [$Cu(OTf)_2$] and copper(II) acetylacetonate [$Cu(acac)_2$], are stable, cheap, and convenient to use; however, reactions with these salts require heat or a reducing reagent to generate Cu(I) in situ.[3]

Recently, we reported that the intermolecular aromatic substitution of an *N*,*N*-disubstituted aniline with α-aryl diazoester **1** proceeded in the presence of a Cu(II)–acid catalyst such as $Cu(OTf)_2$ or a co-catalyst derived from $Cu(acac)_2$ and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) (Scheme 1, Eq. 1).[5] None of the expected products derived from the carbenoid generated from **1** were obtained, such as those from C–H insertion at the N-methylene position[6] or ring-expansion via cyclopropanation of the aromatic double bond.[7] These results suggested us that the reaction of **1** with the Cu(II)–acid catalyst generates the Cu-stabilized carbocation **1-Cu⁺**, which is in resonance with Cu-carbenoid **1-Cu** and might be generated efficiently Eq. 2. Compound **1-Cu⁺** reacts with



Scheme 1. Reactions of diazoester **1** with electron-rich compounds in the presence of Cu(II)–acid catalyst.

---

* Corresponding author. Tel.: +81 25 262 7740; fax: +81 25 262 7741.
E-mail address: tayama@chem.sc.niigata-u.ac.jp (E. Tayama).

http://dx.doi.org/10.1016/j.tetlet.2014.03.115
0040-4039/© 2014 Elsevier Ltd. All rights reserved.

electron-rich aromatics by electrophilic aromatic substitution. We focused on the electrophilic character of **1-Cu**$^+$ and decided to apply our method to its reaction with electron-rich alkenes Eq. 3. Herein, we report the cyclopropanation of alkenes **2** bearing an electron-donating group (EDG), such as 1,3-dienamide, with α-aryl diazoester **1** in the presence of the Cu(II)–acid catalyst.

First, we examined the reactions of **1a** (1.0 equiv) with a slight excess of various alkenes **2** (1.1–1.5 equiv) (Table 1). The procedure is straightforward and does not require the slow addition of **1a**. A solution of 1–2 mol % $Cu(OTf)_2$ (Cat. A) or $Cu(acac)_2$–$BF_3{\cdot}OEt_2$ (Cat. B) in dichloromethane was added to a solution of **1a** and **2** in dichloromethane at room temperature in 1 min under an argon atmosphere. The reaction with allylbenzene (**2a**), a simple alkene, did not show adduction because the dimerization of **1a** predominated (entry 1).[8] When the alkene moiety was activated by an EDG such as butoxy (**2b**), the corresponding cyclopropanation product **3ab** was obtained in 46% yield (entry 2).[9] The amino analogues, enamides **2c** and **2d**, also provided products[10] **3ac** and **3ad** in reasonable yields (entries 3–6). To further improve the synthetic utility of this reaction, we attempted to use 1,3-dienyl derivatives as substrates, which would afford synthetically valuable alkenyl cyclopropane derivatives. The reactions of (*E*)-1,3-butadienylsilyl ether **2e**[11] proceeded at positions 3 and 4, and β-cyclopropylenol silyl ether **3ae** was obtained in good yields with high diastereoselectivities (entries 7, 8). The use of the amino analogue, (*E*)-1,3-butadienamide **2f**,[12] also afforded β-cyclopropylenamide **3af** with similar yield, regio-, and diastereoselectivities (entries 9, 10).

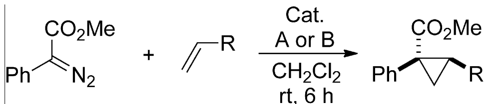
Next, we tested various catalysts to clarify the catalytic activity of $Cu(OTf)_2$ and $Cu(acac)_2$–$BF_3{\cdot}OEt_2$ in the cyclopropanation of **1a** and **2f** (Table 2). The catalyst loading could be reduced to 0.1 mol % (entries 1–3). In the presence of $Cu(acac)_2$ and $BF_3{\cdot}OEt_2$ alone, the reaction did not proceed (entries 4, 5). Cu(I) salts, such as $(MeCN)_4CuPF_6$, catalyzed the reaction without the addition of $BF_3{\cdot}OEt_2$, and the product **3af** was obtained in moderate yield (entry 6). Cu(I) triflate benzene complex $[CuOTf(C_6H_6)_{0.5}]$[13] worked well to give **3af** in 92% yield (entry 7). It is worth noting that the use of rhodium(II) acetate dimer $[Rh_2(OAc)_4]$, which is a standard catalyst in α-diazocarbonyl reactions, resulted in modest yield (entry 8, 51%). The Cu(II)–acid catalyst was found to work as an alternative to previous catalysts, such as Rh, Ru, and Cu(I) complexes, in the reaction of **1a** and **2f**. To expand the substrate scope of our method, **2g** and **2h** were subjected to the reaction conditions. The corresponding product, *N*-diphenylmethyl derivative **3ag** was obtained in similar yields (entries 9, 10); however, the reaction of the *N*-methyl derivative **3ah** showed low yields (entries 11, 12). The acid-catalyzed decomposition of **2h** or **3ah** might occur as a result of instability. The yield was improved using $CuOTf(C_6H_6)_{0.5}$ (entry 13). Although an explanation for this is not entirely clear, it is likely that the Lewis acids interact with $Cu(acac)_2$, making copper more electrophilic, which might allow generation of the Cu-stabilized carbocation **1-Cu**$^+$ depicted in Scheme 1.[14]

To understand the scope and limitations of our proposed reaction, we investigated the reactions of **2f** with various analogs of **1** (Table 3). The reactions using α-(substituted-aryl)diazoesters **1b**–**1g** with **2f** proceeded in reasonable yields through both catalysts A and B (entries 1–12). However, the use of diazoesters without an α-aryl substituent, such as **1h** and **1i**, did not give the adduct **3** (entries 13–16). The Cu-stabilized carbocation **1-Cu**$^+$ could not be generated without an α-aryl substituent.

Thus, an equimolar mixture of α-phenyl diazoester **1a** and α-(*p*-methoxyphenyl)diazoester **1e** was subjected to the Cu(II)–acid catalyzed cyclopropanation of **2f** (Scheme 2). Interestingly enough, product analysis revealed that the reaction with **1e** proceeded preferably to afford **3ef** in 70% yield along with **3af** in 12% yield.

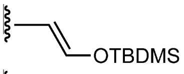
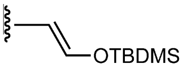
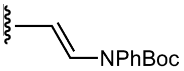
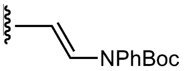
Table 1

Cu(II)–acid catalyzed cyclopropanation of various types of alkene **2** with **1a**[a,b]



1a (1.0 equiv) **2a–2f** (1.1–1.5 equiv) **3aa–3af**

Cat. A: 2 mol% $Cu(OTf)_2$
Cat. B: 1 mol% $Cu(acac)_2$ + 1 mol% $BF_3{\cdot}OEt_2$

Entry	R	Cat.	**3**[c] (%)	Dr[d]
1	CH_2Ph (**2a**)	A	0 (**3aa**)	–
2	O*n*-Bu (**2b**)	A	46 (**3ab**)	>95:5
3	NHCbz (**2c**)	A	93 (**3ac**)	>90:10[e]
4	NHCbz (**2c**)	B	82 (**3ac**)	>90:10[e]
5	NMeCbz (**2d**)	A	53 (**3ad**)	>95:5
6	NMeCbz (**2d**)	B	60 (**3ad**)	>95:5
7	 OTBDMS (**2e**)	A	81 (**3ae**)	90:10
8	 OTBDMS (**2e**)	B	86 (**3ae**)	90:10
9	 NPhBoc (**2f**)	A	89 (**3af**)	90:10
10	 NPhBoc (**2f**)	B	89 (**3af**)	90:10

[a] In entries 1–6, 1.5 equiv of **2** were used. For entries 7–10, 1.1 equiv of **2** were used.

[b] The relative stereochemistries of **3ab**, **3ae**, and **3af** were determined by comparing the ^1H NMR chemical shifts with authentic samples. For details: see the Supplementary data. The relative stereochemistries of **3ac** and **3ad** were tentatively determined by analogy.

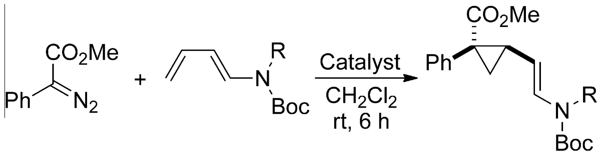
[c] Isolated yield.

[d] Determined by ^1H NMR analysis of the isolated product.

[e] The exact ratio could not be determined because of the formation of rotamers.

Table 2

Cyclopropanation of 1,3-dienamides **2** with **1a** under various conditions[a]



1a

2f (R = Ph)
2g (R = $CHPh_2$)
2h (R = Me)

3af–3ah

Entry	**2**	Catalyst (mol %)	**3**[b] (%)	Dr[c]
1	**f**	$Cu(OTf)_2$ (1)	85 (**3af**)	90:10
2	**f**	$Cu(acac)_2$–$BF_3{\cdot}OEt_2$ (0.5–0.5)	88 (**3af**)	90:10
3	**f**	$Cu(acac)_2$–$BF_3{\cdot}OEt_2$ (0.1–0.1)	77 (**3af**)	90:10
4	**f**	$Cu(acac)_2$ (1)	0 (**3af**)	–
5	**f**	$BF_3{\cdot}OEt_2$ (1)	0 (**3af**)	–
6	**f**	$Cu(MeCN)_4PF_6$ (2)	67 (**3af**)	95:5
7	**f**	$CuOTf(C_6H_6)_{0.5}$ (2)	92 (**3af**)	90:10
8	**f**	$Rh_2(OAc)_4$ (2)	51 (**3af**)	90:10
9	**g**	$Cu(OTf)_2$ (2)	83 (**3ag**)[d]	85:15
10	**g**	$Cu(acac)_2$–$BF_3{\cdot}OEt_2$ (1–1)	86 (**3ag**)[d]	90:10
11	**h**	$Cu(OTf)_2$ (2)	45 (**3ah**)[d]	90:10
12	**h**	$Cu(acac)_2$–$BF_3{\cdot}OEt_2$ (1–1)	10 (**3ah**)[d]	90:10
13	**h**	$CuOTf(C_6H_6)_{0.5}$ (2)	75 (**3ah**)[d]	90:10

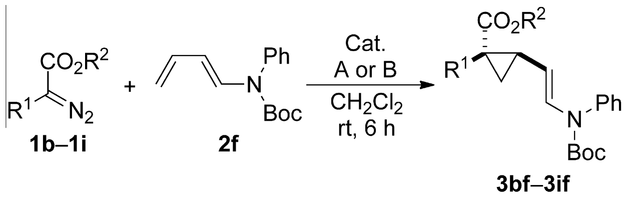
[a] 1.0 equiv of **1a** and 1.1 equiv of **2** were used.

[b] Isolated yield.

[c] Determined by ^1H NMR analysis of the isolated product.

[d] The relative stereochemistries of **3ag** and **3ah** were tentatively determined by analogy with **3af**.

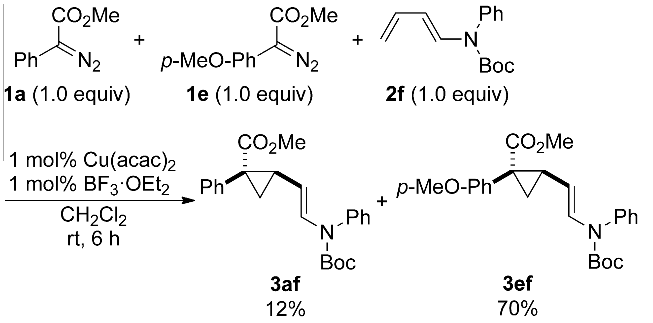
Table 3
Cu(II)–acid catalyzed cyclopropanation of **2f** with various types of **1**[a,b]



Cat. A: 2 mol% $Cu(OTf)_2$
Cat. B: 1 mol% $Cu(acac)_2$ + 1 mol% $BF_3{\cdot}OEt_2$

Entry	R^1	R^2	Cat.	**3**[c] (%)	Dr[d]
1	*p*-Me-Ph (**b**)	Me	A	77 (**3bf**)	95:5
2	*p*-Me-Ph (**b**)	Me	B	85 (**3bf**)	90:10
3	*p*-Cl-Ph (**c**)	Me	A	92 (**3cf**)	90:10
4	*p*-Cl-Ph (**c**)	Me	B	89 (**3cf**)	90:10
5	*p*-Br-Ph (**d**)	Me	A	78 (**3df**)	90:10
6	*p*-Br-Ph (**d**)	Me	B	86 (**3df**)	90:10
7	*p*-MeO-Ph (**e**)	Me	A	81 (**3ef**)	95:5
8	*p*-MeO-Ph (**e**)	Me	B	72 (**3ef**)	95:5
9	*o*-Me-Ph (**f**)	Me	A	71 (**3ff**)	90:10
10	*o*-Me-Ph (**f**)	Me	B	72 (**3ff**)	90:10
11	*m*-Me-Ph (**g**)	Me	A	92 (**3gf**)	90:10
12	*m*-Me-Ph (**g**)	Me	B	88 (**3gf**)	90:10
13[e]	Ac (**h**)	*c*-Hex	A	0	–
14[e]	Ac (**h**)	*c*-Hex	B	0	–
15[e]	H (**i**)	*c*-Hex	A	0	–
16[e]	H (**i**)	*c*-Hex	B	0	–

[a] Unless otherwise noted, 1.0 equiv of **1** and 1.1 equiv of **2f** were used.
[b] The relative stereochemistries of **3bf–3gf** were determined by analogy.
[c] Isolated yield.
[d] Determined by ^1H NMR analysis of the isolated product.
[e] 1.5 equiv of **1h** or **1i** were used.

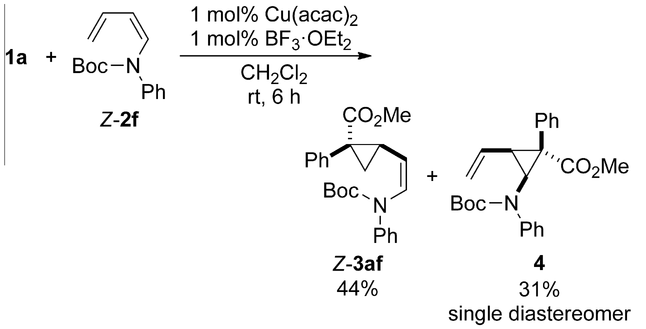


Scheme 2. Cu(II)–acid catalyzed cyclopropanation of **2f** with an equimolar mixture of **1a** and **1e**.

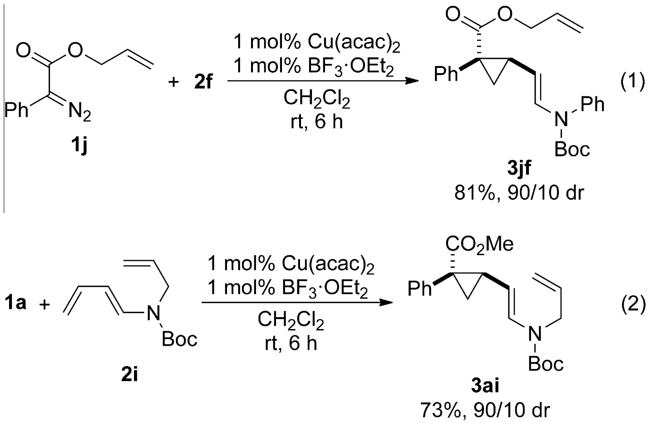
This observation suggests that the Cu-stabilized carbocation **1-Cu**$^+$ derived from **1e** might be generated more efficiently by the electron-donating resonance effect of the *p*-methoxy substituent. The exact intermediate in the cyclopropanation step remains unclear at present (**1-Cu**$^+$ or Cu-carbenoid **1-Cu**), it is safe to say that **1-Cu**$^+$ actually intervenes in the Cu(II)–acid catalyzed cyclopropanation.

The same reaction of the 1*Z*-counterpart of **2f** (*Z*/*E* = 97:3) afforded the corresponding geometric isomer *Z*-**3af** in 44% yield with high stereoselectivity (*E*-**3af** was obtained in ca. 3% yield) along with the 1,2-adduct **4** in 31% yield (Scheme 3). The exact reason for this regioselectivity cannot be explained at present.

Finally, we applied this method for the reaction of **1** and **2** with an allyl substituent, which may react under standard cyclopropanation conditions (Scheme 4). The *O*-allyl ester moiety, as in **1j**, was not affected.[15] The desired cyclopropanation product **3jf** was obtained in 81% yield with 90:10 dr Eq. 1. Furthermore, the *N*-allyl substituent, as in **2i**, also was not affected with **1a**. The corresponding product **3ai** was obtained in 73% yield with 90:10 dr Eq. 2.



Scheme 3. Cu(II)–acid catalyzed cyclopropanation of 1*Z* counterpart of **2f**. Reaction conditions: 1.0 equiv of **1a** and 1.1 equiv of *Z*-**2f** were used. Stereochemistry: The relative stereochemistry of *Z*-**3af** was determined by analogy with **3af**. The relative stereochemistry of **4** was determined by NMR study. For details: see the Supplementary data.



Scheme 4. Cu(II)–acid catalyzed cyclopropanation of *O*- and *N*-allyl derivatives. Reaction conditions: 1.0 equiv of **1** and 1.1 equiv of **2** were used. Stereochemistry: The relative stereochemistries of **3jf** and **3ai** were determined by analogy with **3af**.

In conclusion, we have developed the Cu(II)–acid-catalyzed cyclopropanation of electron-rich alkenes with α-aryl diazoesters. The reaction could be performed without rare metal catalysts, excess substrate, and or experimental difficulty. Further studies of other Cu(II)–acid catalyzed reactions will be reported in due course.

Acknowledgement

This work was supported by the JGC-S Scholarship Foundation (No.1307).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.115.

References and notes

1. Reviews: (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050; (b) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons: New York, 1998.
2. Reviews of Cu-catalyzed cyclopropanation with diazo compounds: (a) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, 10162–10173; (b) Kirmse, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1088–1093.

3. Mechanistic studies of Cu(I) complexes in cyclopropanation with diazo compounds and the in situ generation of Cu(I) from Cu(II) complexes: (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726–728; (b) Dauben, W. G.; Hendricks, R. T.; Luzzio, M. J.; Ng, H. P. *Tetrahedron Lett.* **1990**, *31*, 6969–6972; (c) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005–6008; (d) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553–1565; (e) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839–1844; (f) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300–3310.
4. Qu, Z.; Shi, W.; Wang, J. *J. Org. Chem.* **2001**, *66*, 8139–8144.
5. (a) Tayama, E.; Ishikawa, M.; Iwamoto, H.; Hasegawa, E. *Tetrahedron Lett.* **2012**, *53*, 5159–5161; (b) Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. *Eur. J. Org. Chem.* **2010**, 6719–6721.
6. Selected examples: (a) Davies, H. M. L.; Ni, A. *Chem. Commun.* **2006**, 3110–3112; (b) Davies, H. M. L.; Jin, Q. *Org. Lett.* **2004**, *6*, 1769–1772.
7. Reviews: (a) Reisman, S. E.; Nani, R. R.; Levin, S. *Synlett* **2011**, 2437–2442; (b) McNamara, O. A.; Maguire, A. R. *Tetrahedron* **2011**, *67*, 9–40.
8. When the reaction was performed in the presence of 2 mol % $CuOTf(C_6H_6)_{0.5}$, the same result was obtained. Use of 2 mol % $Rh_2(OAc)_4$ afforded the corresponding cyclopropanation product in 15% yield.
9. Selected examples of Cu-catalyzed cyclopropanation of enol ethers with α-diazoesters: (a) Ebinger, A.; Heinz, T.; Umbricht, G.; Pfaltz, A. *Tetrahedron* **1998**, *54*, 10469–10480; (b) Schumacher, R.; Dammast, F.; Reißig, H.-U. *Chem. Eur. J.* **1997**, *3*, 614–619; (c) Reissig, H.-U.; Reichelt, I.; Kunz, T. *Org. Synth.* **1993**, *71*, 189; (d) Radunz, H.-E.; Reißig, H.-U.; Schneider, G.; Riethmüller, A. *Liebigs Ann. Chem.* **1990**, 705–707; (e) Kunz, T.; Janowitz, A.; Reißig, H.-U. *Synthesis* **1990**, 43–47; (f) Kunkel, E.; Reichelt, I.; Reißig, H.-U. *Liebigs Ann. Chem.* **1984**, 512–530; (g) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44–52.
10. Examples of the cyclopropanation of enamides (and enamines) with α-diazoesters: (a) Chanthamath, S.; Nguyen, D. T.; Shibatomi, K.; Iwasa, S. *Org. Lett.* **2013**, *15*, 772–775; (b) Simone, F. D.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J. *Chem. Eur. J.* **2011**, *17*, 14527–14538; (c) Lu, T.; Song, Z.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 541–544; (d) Melby, T.; Hughes, R. A.; Hansen, T. *Synlett* **2007**, 2277–2279; (e) Miller, J. A.; Hennessy, E. J.; Marshall, W. J.; Scialdone, M. A.; Nguyen, S. T. *J. Org. Chem.* **2003**, *68*, 7884–7886; (f) Arenare, L.; Caprariis, P. D.; Marinozzi, M.; Natalini, B.; Pellicciari, R. *Tetrahedron Lett.* **1994**, *35*, 1425–1426; (g) Paulini, K.; Reißig, H.-U. *Liebigs Ann. Chem.* **1991**, 455–461.
11. Example of the cyclopropanation of 1,3-dienyl ethers with α-diazoesters: (a) Hahn, N. D.; Nieger, M.; Dötz, K. H. *Eur. J. Org. Chem.* **2004**, 1049–1056; (b) Davies, H. M. L.; Peng, Z.-Q.; Houser, J. H. *Tetrahedron Lett.* **1994**, *35*, 8939–8942.
12. Prepared by our method (1,4-elimination): Tayama, E.; Sugai, S. *Tetrahedron Lett.* **2007**, *48*, 6163–6166.
13. Use of $CuOTf(C_6H_6)_{0.5}$ as a Lewis acid: Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, *103*, 861–867.
14. Recently, Reisman's group reported that electron-deficient Cu(II) salts catalyzed the cyclopropanation of aromatic double bonds under heated conditions: (a) Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7304–7311; (b) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774–776; (c) Levin, S.; Nani, R. R.; Reisman, S. E. *Org. Lett.* **2010**, *12*, 780–783.
15. Intramolecular cyclopropanation of *O*-allylic diazophenylacetate: (a) Doyle, M. P.; Hu, W.; Weathers, T. M., Jr *Chirality* **2003**, *15*, 369–373; (b) Doyle, M. P.; Hu, W. *Adv. Synth. Catal.* **2001**, *343*, 299–302; (c) Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145–1147.