

# Silver Triflate-Catalyzed Cyclopropenation of Internal Alkynes with Donor-/Acceptor- Substituted Diazo Compounds

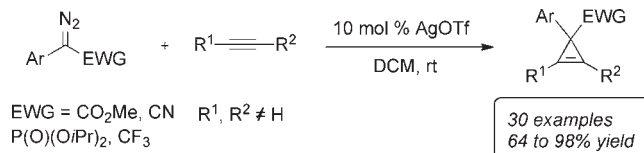
John F. Briones and Huw M. L. Davies\*

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia  
30322, United States

hmdavie@emory.edu

Received June 3, 2011

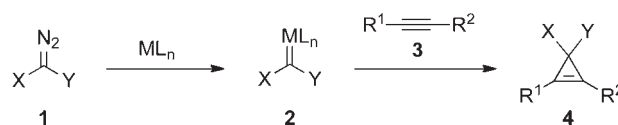
## ABSTRACT



Silver triflate was found to be an efficient catalyst for the cyclopropenation of internal alkynes using donor/acceptor-substituted diazo compounds as carbenoid precursors. Highly substituted cyclopropenes, which cannot be synthesized directly *via* rhodium(II)-catalyzed carbenoid chemistry, can now be readily accessed.

Cyclopropenes continue to attract attention from the synthetic community because of their versatility as building blocks for an array of interesting reactions.<sup>1</sup> These carbocycles are highly strained, which causes them to undergo useful transformations that are thermodynamically unfavorable for typical olefins.<sup>2</sup> One of the most general approaches for the synthesis of cyclopropenes **4** involves the reaction of alkynes **3** with metal carbenoids **2** generated from diazo compounds **1** (Scheme 1).<sup>3</sup>

## Scheme 1



Three major classes of carbenoids have been used in cyclopropenation reactions; acceptor carbenoids, acceptor/acceptor carbenoids, and donor/acceptor carbenoids.<sup>3</sup> The outcome of the reaction is dependent on whether the alkyne is a terminal alkyne or a disubstituted alkyne. Acceptor carbenoids, such as those derived from ethyl diazoacetate, are very reactive and will cyclopropenate both terminal and disubstituted alkynes. The early studies with ethyl diazoacetate used copper(I) salts at elevated

(4) Protopova, M. N.; Shapiro, E. A. *Russ. Chem. Rev.* **1989**, *58*, 667.

(5) For recent Cu-catalyzed cyclopropenation, see: (a) Diaz-Requejo, M. M.; Mairena, M. A.; Beldarrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *Chem. Commun.* **2001**, 1804. (b) Rodriguez, P.; Caballero, A.; Diaz-Requejo, M. M.; Nicasio, M. C.; Perez, P. J. *Org. Lett.* **2006**, *8*, 557. (c) Park, E. J.; Kim, S. H.; Chang, S. J. *Am. Chem. Soc.* **2008**, *130*, 17268.

(1) For reviews on cyclopropenes, see: (a) Padwa, A. *Acc. Chem. Res.* **1979**, *12*, 310. (b) Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271. (c) Walsh, R. *Chem. Soc. Rev.* **2005**, *34*, 714. (d) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117.

(2) (a) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719. (b) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295. (c) Trost, B. M. *Angew. Chem.* **1986**, *98*, 1. (d) Ito, K.; Saito, K. *Recent Res. Dev. Pure Appl. Chem.* **2000**, *4*, 81. (e) *Methods of Organic Chemistry (Houben-Weyl)*, Vol. E17; de Meijere, A., Ed.; Thieme: Stuttgart, 1996. (f) Baird, M. S. *Top. Curr. Chem.* **1988**, *144*, 139. (g) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198. (h) Diev, V.; Kostikov, R.; Gleiter, R.; Molchanov, A. P. *J. Org. Chem.* **2006**, *71*, 4006. (i) Tarwade, V.; Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382. (j) Padwa, A.; Fryxell, G. E. *Cyclization Reactions of Cyclopropenes*. In *Advances in Strain in Organic Chemistry*, Vol. 1; Halton, B., Ed.; Jai Press: Greenwich, CT, 1991.

(3) (a) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221.

temperatures (90–140 °C),<sup>4,5</sup> but the copper catalysts have been largely supplanted by dirhodium catalysts, which form the cyclopropenes under very mild conditions.<sup>6,7</sup> In recent years, several chiral dirhodium catalysts have been developed for asymmetric cyclopropanation with acceptor carbenoids.<sup>8</sup>

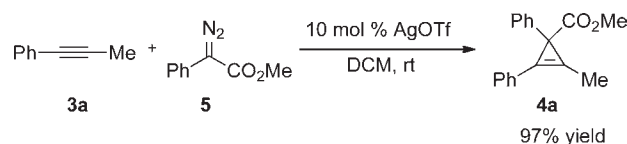
Effective cyclopropanation with acceptor/acceptor carbenoids and donor/acceptor carbenoids is a more recent development compared to the reactions with acceptor carbenoids.<sup>9,10</sup> Highly enantioselective cyclopropanation of terminal alkynes has been achieved with cobalt,<sup>9a</sup> iridium,<sup>9b</sup> and rhodium<sup>10a–c</sup> catalysts, but the reactions fail with disubstituted alkynes.<sup>10a</sup> Computational studies of dirhodium catalysts indicate that the alkyne has close to an end-on approach to the carbenoid with a deviation of 18.2° that would cause a steric clash for a disubstituted alkyne. Furthermore the terminal hydrogen of the alkyne interacts with the carboxylate ligands in the transition state for cyclopropanation with donor/acceptor carbenoids. This may explain why donor/acceptor carbenoids do not cyclopropanate internal alkynes.<sup>10c</sup>

A potential way to overcome this limitation would be to use more reactive types of donor/acceptor carbenoids. Studies have shown that silver catalysts result in effective reactions with donor/acceptor carbenoids.<sup>11</sup> These silver carbenoids do not undergo Wolff rearrangements, which is a common outcome for the silver catalyzed reactions of acceptor carbenoids.<sup>12,13</sup> Moreover, silver catalysts will induce cyclopropanation by donor/acceptor carbenoids of highly substituted olefins which were unreactive under rhodium-catalyzed conditions.<sup>11a</sup> In this paper, we describe that silver catalysis is an excellent approach for the cyclopropanation of internal alkynes with donor/acceptor carbenoids.

We commenced the study by investigating the use of various readily available silver salts in the cyclopropanation of 1-phenyl-1-propyne **3a** with methyl phenyldiazoacetate **5**. Indeed, cyclopropene **4a** was obtained in excellent

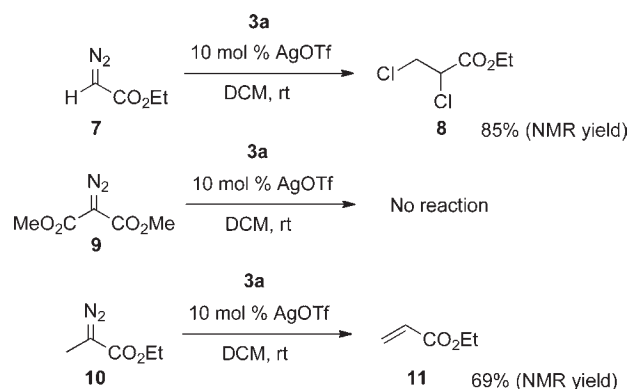
yields using 10 mol % of silver(I) salts having loosely bound counterions with silver triflate providing the highest yield of 97% (Scheme 2). Only trace amounts of cyclopropene product were obtained when silver(I) salts of more tightly bound counterions (i.e., NO<sub>3</sub><sup>−</sup>, PO<sub>4</sub><sup>3−</sup>, CF<sub>3</sub>CO<sub>2</sub><sup>−</sup>, CO<sub>3</sub><sup>2−</sup>, PhCO<sub>2</sub><sup>−</sup>, SO<sub>4</sub><sup>2−</sup>) were used as a catalyst. These results were consistent with the trend observed in the silver-catalyzed cyclopropanation of styrene with **5**.<sup>11a</sup>

Scheme 2



Acceptor- and acceptor-/acceptor-substituted diazo compounds were also utilized as carbenoid precursors to determine the effect of the carbenoid structure on the silver-catalyzed reactions (Scheme 3). Ethyl diazoacetate **7** failed to undergo cyclopropanation with **3a**. Instead C–Cl insertion occurred into the solvent dichloromethane to produce the dichloro derivative **8** in 85% yield. Similar reactivity has been reported for silver scorpionate catalysts.<sup>14</sup> Diazomalonate also did not afford the desired cyclopropene products. The <sup>1</sup>H NMR analysis of the crude reaction mixture showed that the diazo compounds remained unchanged. Silver complexes are known to be capable of forming thermally stable complexes with diazo compounds

Scheme 3



containing two electron-withdrawing groups,<sup>15,16</sup> and this may explain the lack of reactivity with these systems. Ethyl-2-diazopropanoate **10** was converted to ethyl

(6) Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssie, Ph. *Tetrahedron Lett.* **1978**, 1239.

(7) For reviews, see: (a) Doyle, M. P. *Russ. Chem. Bull.* **1994**, *43*, 1770. (b) Doyle, M. P. *Pure Appl. Chem.* **1998**, *70*, 1123. (c) Doyle, M. P. *Enantiomer* **1999**, *4*, 621. (d) Doyle, M. P.; Hu, W. *Synlett* **2001**, *43*, 5997.

(8) (a) Doyle, M. P.; Winchester, W. P.; Hoorn, J. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968. (b) Doyle, M. P.; Protopova, M.; Muller, P.; Enc, D.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492. (c) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 1803.

(9) For cyclopropanation with acceptor-/acceptor-substituted diazo compounds, see: (a) Cui, X.; Xu, X.; Lu, H.; Zhu, S.; Wojtas, L.; Zhang, P. X. *J. Am. Chem. Soc.* **2011**, *133*, 3304. (b) Uehara, M.; Suetatsu, H.; Yasutomi, Y.; Katsuki, T. *J. Am. Chem. Soc.* **2011**, *133*, 170.

(10) For cyclopropanation with donor-/acceptor-substituted diazo compounds, see: (a) Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2004**, *6*, 1233. (b) Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211. (c) Briones, J. F.; Davies, H. M. L. *Tetrahedron* **2011**, *67*, 4313.

(11) (a) Thompson, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090. (b) Hansen, J. H.; Davies, H. M. L. *Chem. Sci.* **2011**, *2*, 457. (c) Yue, Y.; Wang, Y.; Hu, W. *Tetrahedron Lett.* **2007**, *48*, 3975.

(12) For a review on Wolff rearrangement involving silver salts, see: Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.

(13) For recent examples on silver-catalyzed Wolff rearrangement, see: (a) Seki, H.; Georg, G. I. *J. Am. Chem. Soc.* **2010**, *132*, 15512. (b) Seki, H.; Georg, G. I. *Org. Lett.* **2011**, *13*, 2147.

(14) Dias, H. V. R.; Browning, R. G.; Polach, S. A.; Diyabalanage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9270.

(15) Julian, R. R.; May, J. A.; Stoltz, B. M.; Beauchamp, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 4478.

(16) Dias, H. V. R.; Polach, S. A. *Inorg. Chem.* **2000**, *39*, 4676.

acrylate **11**, the product of a  $\beta$ -hydride elimination in 69% yield, although, under rhodium catalysis, effective cyclopropenation can be achieved with **10**.<sup>17</sup> These results are consistent with the hypothesis that silver carbenoids behave as more reactive intermediates than the rhodium carbenoids,<sup>11a</sup> and it is only in the case of donor/acceptor carbenoids that the carbenoid is sufficiently stabilized for effective cyclopropenation to occur.

The generality of the silver-catalyzed cyclopropenation was investigated with a range of disubstituted alkynes, and the cyclopropene products were obtained in good to excellent yields (Table 1). The structure of cyclopropene **4b** was confirmed by X-ray crystallography.<sup>18</sup> 1,2-Diaryl alkynes (entries 12–15) were effectively cyclopropenated (64–98%). Cyclopropenation of alkyne with a boronic ester functionality was achieved, as in the case of entry 14. Monocyclopropenation of 1,3-diyne was also a viable process affording the alkynyl cyclopropene **4p**. It is also interesting to note that the cyclopropenation reaction is very chemoselective as C–H insertion at the benzylic site (entries 7, 9–11) as well as the methylene site next to siloxy groups (entries 8 and 17) was not observed. Terminal alkynes such as phenylacetylene and 1-TMS-phenylacetylene (entries 18 and 19) did not afford the desired cyclopropenes. The reactions with these substrates resulted in the formation of precipitates. It is well-known that terminal alkynes react with silver salts to form insoluble silver acetylides,<sup>19</sup> and this may be the reason for unproductive cyclopropenation of the terminal alkyne.

Several substrates were tested to further determine the chemoselectivity of the AgOTf-catalyzed reaction in more functionalized systems (Table 2). Substrates that contain both alkyne and alkene moieties were tested to determine whether cyclopropenation would be more favored over cyclopropanation. In the case of entry 1, only the cyclopropanation product **13** was obtained as a single diastereomer. The relative configuration of **13** was assigned based on NOE analysis. Interestingly, when the olefin is more highly substituted, the reaction favors the formation of the cyclopropene **15** in 85% yield. In the case of entry 3, cyclopropene **17** was isolated in excellent yield (86%). Only a trace amount of the product from the cyclopropanation of the electronically neutral and unsubstituted olefin was observed.

The scope of the AgOTf-catalyzed cyclopropenation was further examined by utilizing various donor-/acceptor-substituted diazo compounds with 1-phenyl-1-propyne **3a** as the representative alkyne trap (Table 3). Excellent yields of the cyclopropene were obtained using both electron-poor and relatively electron-rich aryldiazoacetates. However, cyclopropenation was not observed in the case of *p*-methoxyphenyl diazoacetate (entry 12) reflecting the low reactivity of the *p*-methoxyphenyl carbenoid

(17) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22.

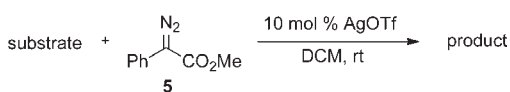
(18) The crystal structure of **4b** have been deposited at the Cambridge Crystallographic Data Centre, and the deposition numbers CDCC 827875 have been allocated.

(19) (a) Letinois-Halbes, U.; Pale, P.; Berger, S. *J. Org. Chem.* **2005**, *70*, 9185. (b) Viterisi, A.; Orsini, A.; Weibel, J. M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 2779. (c) Bruce, M. I.; Humphrey, M. G.; Matisons, J. G.; Roy, S. K.; Swincer, A. G. *Aust. J. Chem.* **1984**, *37*, 1955.

**Table 1.** Silver-Catalyzed Cyclopropenation of Various Alkynes with Methyl Phenyl diazoacetate **5**<sup>a</sup>

$\text{R}^1\text{—C}\equiv\text{C—R}^2 + \text{Ph—C(=N}_2\text{)—CO}_2\text{Me} \xrightarrow[\text{DCM, rt}]{10 \text{ mol \% AgOTf}} \text{Ph—C(CO}_2\text{Me)—C(R}^1\text{)=C(R}^2\text{)}$				
entry	R <sup>1</sup>	R <sup>2</sup>	product	yield (%) <sup>b</sup>
1			<b>4a</b>	97
2			<b>4b</b>	91
3			<b>4c</b>	93
4			<b>4d</b>	82
5			<b>4e</b>	68
6			<b>4f</b>	81
7			<b>4g</b>	91
8			<b>4h</b>	84
9			<b>4i</b>	87
10			<b>4j</b>	92
11			<b>4k</b>	86
12			<b>4l</b>	98
13			<b>4m</b>	88
14			<b>4n</b>	64
15			<b>4o</b>	80
16 <sup>c</sup>			<b>4p</b>	92
17			<b>4q</b>	85
18			<b>4r</b>	0
19			<b>4s</b>	0

<sup>a</sup> Reaction conditions: 1 mmol of **3** used in 10 mL of solvent, 0.5 mmol of **5** used. <sup>b</sup> Isolated yield. <sup>c</sup> *p*-Br phenyldiazoacetate used.

**Table 2.** Chemoselectivity Studies: Cyclopropanation vs Cyclopropanation<sup>a</sup>

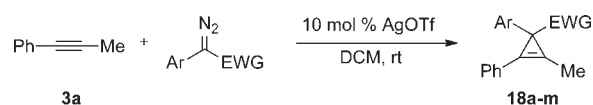
entry	substrate	product	yield (%) <sup>b</sup>
1 <sup>c</sup>			89
2			85
3			86

<sup>a</sup> Reaction conditions: 1 mmol of substrate and 0.5 mmol of **5** used in 10 mL of solvent. <sup>b</sup> Isolated yield. <sup>c</sup> Product **13** formed with >20:1% dr.

even at refluxing conditions. Reaction with sterically demanding diazo compound such as in the case of entry 4 with the substituted *ortho* positions was also a viable process. Varying the electron-withdrawing group on the carbenoid was also possible as the trifluoromethyl-, phosphonate-, and cyano-substituted cyclopropenes were formed in excellent yields (84–98%, entries 9–11). Although methyl styryldiazoacetate has been shown to be an effective carbenoid precursor for Ag(I)-catalyzed cyclopropanation reactions,<sup>11a</sup> it failed to afford the desired cyclopropene product (entry 13). This failure is probably due to product instability.<sup>9a,b</sup>

In summary, we have demonstrated that silver triflate is an effective catalyst for cyclopropanation of disubstituted alkynes using donor-/acceptor-substituted diazo compounds. Highly substituted cyclopropenes that have not been synthesized before are now readily accessible. These studies demonstrate that silver catalysis has advantages in certain cases over rhodium catalysis. Further studies are ongoing to develop suitable chiral silver catalysts, in order to achieve enantioselective variants of the cyclopropanation reactions.

**Acknowledgment.** Financial support of this work by the National Science Foundation is greatly acknowledged. We thank Dr. Kenneth I. Hardcastle for the X-ray crystal structure determination.

**Table 3.** AgOTf-Catalyzed Cyclopropanation of **3a** and Various Diazoacetates<sup>a</sup>

entry	Ar	EWG	product	yield (%) <sup>b</sup>
1		CO <sub>2</sub> Me	<b>18a</b>	93
2		CO <sub>2</sub> Me	<b>18b</b>	91
3		CO <sub>2</sub> Me	<b>18c</b>	90
4		CO <sub>2</sub> Me	<b>18d</b>	83
5		CO <sub>2</sub> Me	<b>18e</b>	92
6		CO <sub>2</sub> Me	<b>18f</b>	81
7		CO <sub>2</sub> Me	<b>18g</b>	82
8		CO <sub>2</sub> Me	<b>18h</b>	87
9		CF <sub>3</sub>	<b>18i</b>	84
10		CN	<b>18j</b>	93
11		P(O)(O <i>i</i> Pr) <sub>2</sub>	<b>18k</b>	98
12 <sup>c</sup>		CO <sub>2</sub> Me	<b>18l</b>	0
13		CO <sub>2</sub> Me	<b>18m</b>	0

<sup>a</sup> Reaction conditions: 1 mmol of **3a** used in 10 mL of solvent, 0.5 mmol of aryldiazo used. <sup>b</sup> Isolated yield. <sup>c</sup> <sup>1</sup>H NMR analysis of the crude reaction mixture showed formation of carbene dimers.

**Supporting Information Available.** Detailed experimental procedures and full characterization including <sup>1</sup>H and <sup>13</sup>C spectra for all new compounds. This material is available free of charge *via* the Internet at <http://pubs.acs.org>.