JOC*Note*

Stereoselective Formation of Alkenyl Halides via Magnesium Halide Promoted Ring Opening of Bis-Activated Cyclopropenes

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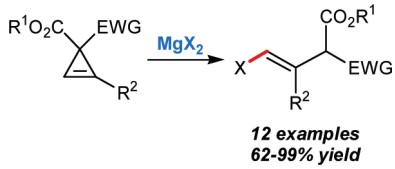
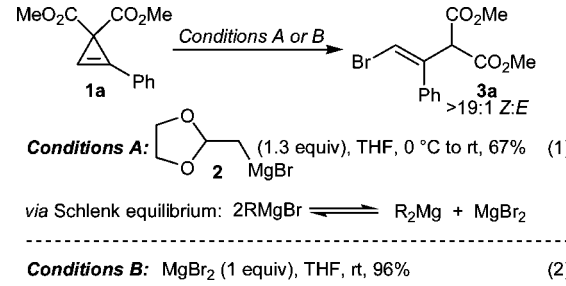


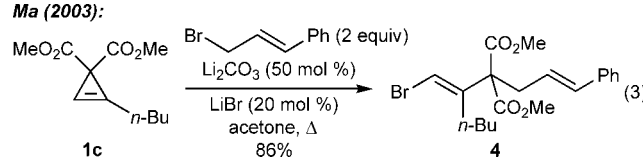
In the presence of stoichiometric magnesium halides, a range of bis-activated cyclopropenes undergo highly stereoselective ring-opening reactions to produce multisubstituted alkenyl halides. More highly functionalized compounds may be obtained by trapping of the magnesium enolate intermediates in situ.

Cyclopropenes, the smallest unsaturated carbocycles, are an important class of building blocks for organic synthesis.[1] The high strain energy stored within the three-membered ring of cyclopropenes may be harnessed in the design of novel chemical transformations that are often unavailable to simple alkenes.[1,2] For example, cyclopropenes are highly susceptible to a broad range of addition reactions across the double bond[1b] to provide functionalized cyclopropanes, which themselves are important targets and common structural components in numerous biologically active natural products and pharmaceuticals.[3] The strain energy of cyclopropenes may also be exploited in a host of cycloaddition and rearrangement reactions, providing numerous other molecules of interest.[1]

During our recent investigations into the development of stereoselective carbometalation−ring-opening reactions of bis-activated cyclopropenes to produce multisubstituted alkenes,[2d] the reaction of cyclopropene **1a** with commercially available Grignard reagent **2** was conducted (eq 1). Instead of furnishing products derived from addition of the nucleophilic alkyl functionality of **2**, the major product isolated in this reaction was the alkenyl bromide **3a**. We attributed this initially surprising result to reaction of cyclopropene **1a** with magnesium bromide produced from the Schlenk equilibrium[4] of the Grignard reagent. This hypothesis was supported by reaction of **1a** with $MgBr_2$ itself, which also produced **3a**, but in 96% yield (eq 2).



This process is closely related to the results of Ma and coworkers, who described a series of alkali metal halide induced cyclopropene ring-opening−alkylation reactions that required an alkali metal carbonate additive for highest yields (representative example shown in eq 3).[5a] However, their process differs from ours in that simple protonolysis of the initial ring-opened species was not described in their work.[5a] The majority of examples described by Ma were conducted using a bis-activated cyclopropene that was unsubstituted at the alkene, although four results using trisubstituted cyclopropenes were reported (as in eq 3).[5a]



To establish whether the serendipitous result of eq 2 could be translated into a general and efficient process, a range of bis-activated cyclopropenes **1a**−**1g** were reacted with stoichiometric quantities of magnesium halides, and these results are presented in Table 1. Using $MgBr_2$, cyclopropenes **1a**−**1e** containing alkyl or aryl functionality on the alkene efficiently underwent the ring-opening reaction to provide alkenyl bromides

(1) For reviews, see: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77–151. (b) Baird, M. S. *Cyclopropenes: Transformations (Houben-Weyl)*; Thieme: Stuttgart, Germany, 1997; Vol. E17d/2, pp 2781−2790. (c) Nakamura, M.; Isabe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295–1326. (d) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719–732. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221–1245. (f) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (g) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364–7376.

(2) For recent, selected examples of investigations into the reactivity of cyclopropenes, see: (a) Fisher, L. A.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 8474–8478. (b) Sherill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804–13809. (c) Fordyce, E. A. F.; Luebbers, T.; Lam, H. W. *Org. Lett.* **2008**, *10*, 3993–3996. (d) Wang, Y.; Fordyce, E. A. F.; Chen, F. Y.; Lam, H. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7350–7353. (e) Pallerla, M. K.; Yap, G. P. A.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 6137–6141. (f) Alnasleh, B. K.; Sherrill, W. M.; Rubin, M. *Org. Lett.* **2008**, *10*, 3231–3234. (g) Yan, N.; Liu, X.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 563–568. (h) Fordyce, E. A. F.; Wang, Y.; Luebbers, T.; Lam, H. W. *Chem. Commun.* **2008**, 1124–1126. (i) Rubina, M.; Woodward, E. W.; Rubin, M. *Org. Lett.* **2007**, *9*, 5501–5504. (j) Masarwa, A.; Stanger, A.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 8039–8042. (k) Trofimov, A.; Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Org. Chem.* **2007**, *72*, 8910–8920. (l) Chuprakov, S.; Malyshev, D. A.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 14868–14869. (m) Hirashita, T.; Shiraki, F.; Onishi, K.; Ogura, M.; Araki, S. *Org. Biomol. Chem.* **2007**, *5*, 2154–2158. (n) Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 3824–3825.

(3) (a) Liu, H. W.; Walsh, C. T. Biochemistry of the Cyclopropyl Group In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 1987; pp 959−1025. (b) Salaun, J. *Top. Curr. Chem.* **2000**, *207*, 1–67.

(4) Schlenk, W.; Schlenk, W., Jr. *Chem. Ber.* **1929**, *62*, 920–924.

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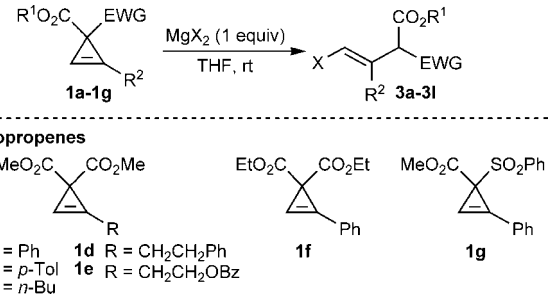
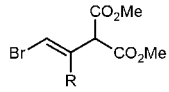
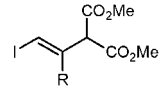
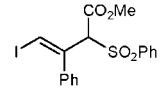
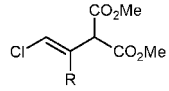
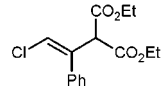
TABLE 1. Magnesium Halide Mediated Ring Openings of Various Cyclopropenes[a]

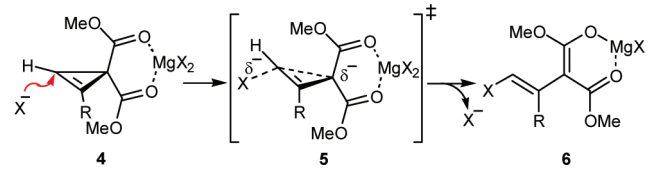


entry	MgX_2	substrate	product		yield (%)
1	$MgBr_2$	**1a**		R = Ph **3a**	96[b]
2		**1b**		R = *p*-Tol **3b**	72
3		**1c**		R = *n*-Bu **3c**	75
4		**1d**		R = CH_2CH_2Ph **3d**	87
5		**1e**		R = CH_2CH_2OBz **3e**	84
6	MgI_2	**1a**		R = Ph **3f**[c]	97
7		**1b**		R = *p*-Tol **3g**	94
8		**1d**		R = CH_2CH_2Ph **3h**	99
9		**1g**		**3i**	77
10[d]	$MgCl_2$	**1b**		R = *p*-Tol **3j**[e]	83
11[d]		**1c**		R = *n*-Bu **3k**[e]	85
12[d]		**1f**		**3l**	62

[a] Reactions were carried out using 0.20 mmol of cyclopropene in THF (2 mL). [b] A preparative scale reaction conducted using 2.00 mmol of cyclopropene **1a** in THF (20 mL) also provided **3a** in 96% yield. [c] Product isolated as an inseparable 9:1 *Z*:*E* mixture. [d] Reaction conducted at 40 °C. [e] The product was accompanied by ca. 6% of an inseparable regioisomeric impurity.

3a−**3e**, respectively, in good yields and with high stereoselectivities[6] (entries 1−5). In all cases, the bromide anion attacked the least substituted carbon of the alkene with high selectivity, though small quantities of regioisomeric products were observed in a few cases (entries 10 and 11). This regioselectivity is opposite to that seen in the large majority of cyclopropene carbometalation and hydrometalation reactions described previously[1d] but is consistent with the results of Ma and co-workers (eq 3).[5a] Ring openings with MgI_2 and $MgCl_2$ also occurred smoothly to furnish alkenyl halides **3f**−**3l** (entries 6−12), though a reaction temperature of 40 °C was required in the case of $MgCl_2$ (entries 10−12). The ability to prepare alkenyl chlorides is notable since this feature was not reported previously.[5a] In addition to dimethyl malonate derived substrates **1a**−**1e**, cyclopropenes **1f** and **1g** containing ethyl esters or a phenylsulfone, respectively, were competent substrates (entries 9 and 12). Unfortunately, no reaction occurred when MgF_2 was employed, presumably due to the low solubility of this salt.[7]

SCHEME 1. Possible Mechanism



The stereochemical outcome of these reactions, where inversion of configuration at the electrophilic vinylic center is observed, suggests that an in-plane S_N2-type mechanism[8,9] (also referred to as $S_NV\sigma$[9e]) is operative, rather than an addition−elimination process similar to that proposed in related cyclopropene carbometalation−ring-opening reactions.[2d] Although $S_NV\sigma$ mechanisms had long been considered to be energetically unfavorable compared to alternative pathways,[10] a growing body of theoretical[8] and experimental[9] work suggests that this process is favorable in certain reactions.

Therefore, a possible mechanism for magnesium halide promoted cyclopropene ring opening, using a dimethyl malonate derived substrate for illustrative purposes, is outlined in Scheme 1. It is likely that bidentate coordination of magnesium halide to the cyclopropene (as in **4**) promotes nucleophilic attack by the halide ion to provide (via transition state **5**) magnesium enolate **6** that is protonated upon workup to furnish the product. This mechanistic scenario suggested that trapping of the magnesium enolates **6** to generate more highly functionalized products might be possible, in similar fashion to the results of Ma and co-workers (eq 3).[5a] Accordingly, various one-pot multicomponent coupling reactions of bis-activated cyclopropenes, magnesium halides, and different electrophiles were investigated. However, we found these enolates to be rather unreactive, though Michael additions to β-unsubstituted enones using acetonitrile as the solvent were possible, without the requirement for additional basic additives (Scheme 2).[5a]

In summary, magnesium halide salts promote ring-opening reactions of bis-activated cyclopropenes to provide trisubstituted alkenyl halides with high stereoselectivities. The magnesium enolates that are produced in these reactions may be trapped with enones to result in more highly functionalized products. Compared with related reactions,[5a] this work extends the scope of the nucleophilic and electrophilic components to encompass chloride anions and enones, respectively, increasing the range of products that may be accessed.

Experimental Section

General Procedure A: Magnesium Halide Mediated Ring Opening of Cyclopropenes. A solution of the appropriate cyclo-

(5) (a) Ma, S.; Zhang, J.; Cai, Y.; Lu, L. *J. Am. Chem. Soc.* **2003**, *125*, 13954–13955. For halide-catalyzed cycloproprene ring-opening−cycloaddition reactions with imines, see: (b) Ma, S.; Zhang, J.; Lu, L.; Jin, X.; Cai, Y.; Hou, H. *Chem. Commun.* **2005**, 909–911.

(6) The stereochemistries of alkenyl halides **3a**, **3d**, **3k**, and **7a** were determined on the basis of NOESY experiments. See Supporting Information for details.

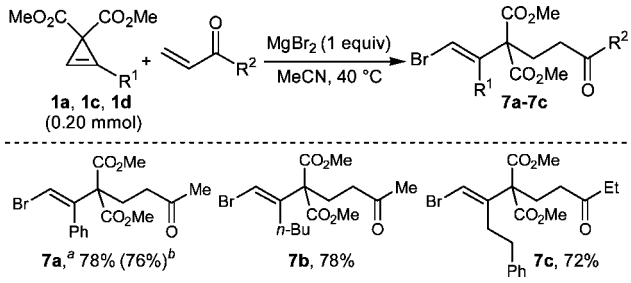
(7) Reactions conducted using other fluoride salts such as ZnF_2, KF, and CsF in THF or MeCN at elevated temperatures also returned unchanged starting material.

(8) (a) Glukhovtsev, M. N.; Pross, A.; Radom, L. *J. Am. Chem. Soc.* **1994**, *116*, 5961–5962. (b) Luchini, V.; Modena, G.; Pasquato, L. *J. Am. Chem. Soc.* **1995**, *117*, 2297–2300. (c) Kim, C. K.; Hyun, K. H.; Kim, C. K.; Lee, I. *J. Am. Chem. Soc.* **2000**, *122*, 2294–2299. (d) Bach, R. D.; Baboul, A. G.; Schlegel, H. B. *J. Am. Chem. Soc.* **2001**, *123*, 5787–5793.

(9) (a) Ochiai, M.; Oshima, K.; Masaki, Y. *J. Am. Chem. Soc.* **1991**, *113*, 7059–7061. (b) Okuyama, T.; Takino, T.; Sato, K.; Ochiai, M. *J. Am. Chem. Soc.* **1998**, *120*, 2275–2282. (c) Ochiai, M.; Nishi, Y.; Hirobe, M. *Tetrahedron Lett.* **2005**, *46*, 1863–1866. (d) Shiers, J. J.; Shipman, M.; Hayes, J. F.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2004**, *126*, 6868–6869. (e) Miyauchi, H.; Chiba, S.; Fukamizu, K.; Ando, K.; Narasaka, K. *Tetrahedron* **2007**, *63*, 5940–5953. See also ref 5a.

(10) Kelsey, D. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 1953–1961.

SCHEME 2. One-Pot Cyclopropene Ring-Opening−Michael Reactions



[a] The product was accompanied by ca. 5% of an inseparable regioisomeric impurity. [b] Yield in parentheses refers to a reaction conducted using 8.00 mmol of cyclopropene **1a**.

propene (0.20 mmol) in THF (1 mL + 1 mL rinse) was added via cannula to a vial containing the appropriate magnesium halide (0.20 mmol) and a stirrer bar. The resulting mixture was stirred at the indicated temperature for the indicated time and then filtered through a short plug of SiO_2 (ca. 4 cm high × 2 cm diameter) using EtOAc as eluent (ca. 50 mL). After the filtrate was concentrated in vacuo, purification of the residue by column chromatography afforded the alkenyl halide product.

(*Z*)-Dimethyl 2-(2-bromo-1-phenylvinyl)malonate (3a). The title compound was prepared according to General Procedure A from cyclopropene **1a** (46 mg, 0.20 mmol) and $MgBr_2$ (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane → 5% EtOAc/hexane) to give a colorless oil (60 mg, 96%): IR (film) 2954, 2846, 1738 (C═O), 1620, 1491, 1437, 1265, 1201, 1151, 1076 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41−7.38 (2H, m), 7.36−7.31 (3H, m), 6.75 (1H, d, J = 0.6 Hz), 4.50 (1H, d, J = 0.6 Hz), 3.76 (6H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 167.1 (2 × C), 138.1 (C), 137.2 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 110.6 (CH), 58.8 (CH), 52.9 (2 × CH_3); HRMS (EI) exact mass calcd for $C_{13}H_{13}{}^{79}BrO_4$ [M^+] 311.9992, found 311.9992.

General Procedure B: One-Pot Magnesium Halide Mediated Ring-Opening−Michael Reactions of Cyclopropenes. A solution of the appropriate cyclopropene (0.20 mmol) in MeCN (1 mL + 1 mL rinse) was added via cannula to a vial containing the appropiate enone (0.40 mmol), $MgBr_2$ (37 mg, 0.20 mmol), and a stirrer bar. The resulting mixture was stirred at 40 °C for 18 h. After cooling to room temperature, the mixture was filtered through a short plug of SiO_2 (ca. 4 cm high × 2 cm diameter) using EtOAc as eluent (ca. 50 mL), and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography afforded the alkenyl halide product.

(*Z*)-Dimethyl 2-(2-bromo-1-phenylvinyl)-2-(3-oxobutyl)malonate (7a). The title compound was prepared according to General Procedure B from cyclopropene **1a** (46 mg, 0.20 mmol) and methyl vinyl ketone (32 μL, 0.40 mmol) and purified by column chromatography (10−30% EtOAc/hexane) to give a colorless oil (60 mg, 78%): IR ($CHCl_3$) 2953, 1735 (C═O), 1613, 1491, 1437, 1366, 1254, 1171, 1092, 1030 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38−7.31 (3H, m), 7.07−7.05 (2H, m), 6.92 (1H, s), 3.71 (6H, s), 2.53−2.50 (2H, m), 2.27−2.24 (2H, m), 2.09 (3H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 206.6 (C), 169.5 (2 × C), 141.4 (C), 137.1 (C), 128.8 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 112.3 (CH), 63.7 (C), 52.8 (2 × CH_3), 39.0 (CH_2), 29.9 (CH_3), 28.2 (CH_2); HRMS (ES) exact mass calcd for $C_{17}H_{20}{}^{79}BrO_5$ [M + H]$^+$ 383.0489, found 383.0492.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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