

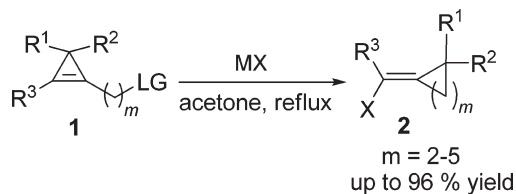
An X⁻ (X = I, Br)-Triggered Ring-Opening
Cyclization of Cyclopropenyl-Substituted Alkyl
Halides or Mesylates: An Efficient and Highly Regio-
and Stereoselective Approach to (*E*)-Haloalkylidene
4–7-Membered Cyclic Compounds

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Polyfunctionalized (*E*)-haloalkylidene cyclic products were efficiently synthesized in moderate to excellent yields via a regio- and stereoselective X⁻ (X = I or Br)-triggered ring-opening intramolecular trapping of cyclopropenes **1**. The reaction can be used for construction of 4–7-membered products. The *E*-stereoselectivity of the *exo*-C=C bond is very high. The carbon–halogen bond in the *exo*-C=C bond may further be elaborated to prepare differently substituted cyclic products with a stereodefined C=C bond.

Efficient synthesis of carbocycles and heterocycles is one of the main themes in organic synthesis due to the importance of cyclic compounds.^{1–3} Recently functionalized

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allenes have been developed as a class of powerful starting materials for the construction of cyclic compounds.⁴ As two classes of very similar analogues to allenes, alkylidenecyclopropanes^{5,6} and even cyclopropenes^{5t,5u,7,8} have also caught the attention of organic chemists.

In 2003, we described a regioselective cycloisomerization of cyclopropenyl ketones leading to 2,3,4-trisubstituted furans or 2,3,5-trisubstituted furans by using CuI or PdCl₂(CH₃CN)₂ as the catalysts, respectively.⁹ In the same year, we noticed an X⁻ (X = I, Br)-triggered ring-opening

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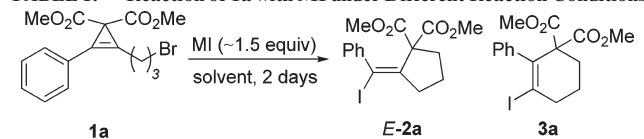
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TABLE 1. Reaction of **1a** with MI under Different Reaction Conditions



entry	MI	solvent	temp (°C)	yield of <i>E-2a</i> ^a (%)
1 ^b	NaI	acetone	reflux	78
2 ^{b,c}	NaI	acetone	reflux	70
3	NaI	acetone	reflux	80
4	AgI	acetone	reflux	0 ^d
5	CuI	acetone	reflux	0 ^e
6	LiI	acetone	reflux	58
7	NaI	CH ₃ CN	reflux	74
8	NaI	THF	reflux	74
9	NaI	CH ₃ NO ₂	80	71
10	NaI	dioxane	80	73
11	NaI	DCE	80	67

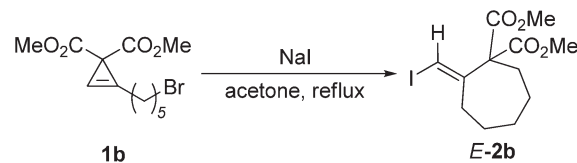
^a Isolated yield. ^b 0.5 equiv of Na₂CO₃ was used. ^c 1.2 equiv of NaI was used. ^d 89% of **1a** was recovered. ^e 83% of **1a** was recovered.

coupling reaction of cyclopropenyl carboxylates with organic halides providing an efficient and highly regio- and stereoselective route to a series of polyfunctionalized (*E*)-alkenyl halides.¹⁰ However, in the presence of imines, the NaI-catalyzed reaction of cyclopropenyl carboxylates provided a highly regio- and stereoselective route to a series of polyfunctionalized vinyl aziridines.¹¹ Herein, we wish to report an X⁻ (X = I, Br)-triggered ring-opening cyclization of cyclopropenyl-substituted alkyl halides or mesylates, providing a highly regio- and stereoselective approach to the synthesis of (*E*)-haloalkylidene 4–7-membered cyclic compounds.

The reaction of dimethyl 2-(3-bromopropyl)-3-phenylcycloprop-2-ene-1,1-dicarboxylate **1a** with 1.5 equiv of NaI in the presence of 0.5 equiv of Na₂CO₃ in acetone under reflux was studied. To our delight, the reaction smoothly led to the formation of (*E*)-iodobenzylidenecyclopentane derivative **E-2a** in 78% yield with excellent regio- and stereoselectivity, which was established by the X-ray diffraction study of **E-2a** (Figure S1, Supporting Information).¹² It should be noted that in all the cases the formation of six-membered ring **3a** was not observed, which indicated that the iodide anion attacked regioselectively at the sp²-carbon atom connected to the phenyl group in **1a**.

With 1.2 equiv of NaI, the yield of **E-2a** is lower (entry 2, Table 1); control experiment indicated that the addition of Na₂CO₃ is not necessary in this case (entry 3, Table 1); no reaction was observed with AgI or CuI (entries 4 and 5, Table 1); the reaction with LiI afforded **E-2a** in much lower

TABLE 2. Reaction of **1b** with NaI under Different Reaction Conditions



entry	NaI (equiv)	additive ^a	M ^b (mol/L)	time (h)	yield of <i>E-2b</i> ^c (%)
1	1.5	none	0.067	18	9
2	1.5	Na ₂ CO ₃ (0.6)	0.067	16.5	23
3	1.7	Na ₂ CO ₃ (0.7)	0.05	20	57
4	1.6	Na ₂ CO ₃ (0.6)	0.025	20	47

^a Equiv of Na₂CO₃ used. ^b M = the concentration of **1b**. ^c Isolated yield.

yield (entry 6, Table 1); study on the solvent effect implied that acetone is the best solvent for this transformation (compare entries 7–11 with entry 3, Table 1).

However, when we applied the optimized reaction conditions to the reaction of 5-(3',3'-bis(methoxycarbonyl)cyclopropenyl)pentyl bromide **1b**, the yield of the 7-membered product **E-2b** was only 9% (entry 1, Table 2). It was observed that the reaction with the addition of 0.6 equiv of Na₂CO₃ afforded **E-2b** in a slightly higher yield (entry 2, Table 2). Thus, further study for the effect of concentration of **1b** was conducted (Table 2). When the concentration of **1b** was adjusted to 0.05 M, we were pleased to find that the reaction of **1b** in the presence of 0.7 equiv of Na₂CO₃ occurred smoothly to give the product **E-2b** in 57% yield (entry 3, Table 2). The stereochemistry was also established by its X-ray diffraction study (Figure S2, Supporting Information).¹³ Here again, the regioselectivity is very high with I⁻ attacking the less substituted sp² carbon atom, which is the same as reported in our previous studies.¹⁰

With the optimized reaction conditions in hand, the scope of the reaction of the mesylates was studied with some of the typical results being summarized in Table 3. R¹ or R² may be COCH₃, CO₂Me, CO₂Et, and SO₂Ph. Besides NaI, LiBr·H₂O may also be used as the metallic halide to give the corresponding (*E*)-bromomethylene 5-membered products in moderate to excellent yields (entries 2, 4, 6, and 8, Table 3). Even the 4-membered product **E-2i** was prepared in 27% yield from the ring-opening reaction of **1h** (entry 10, Table 3).

It should also be noted that 3,3-bis(methoxycarbonyl)-2-alkyl or aryl-substituted cyclopropenylalkyl bromides **1i**, **1j**, and **1k** also smoothly afforded the corresponding products **E-2m**, **E-2n**, and **E-2o** with the excellent regioselectivity directing the X to the sp² carbon atom at the 1-position (Scheme 1).

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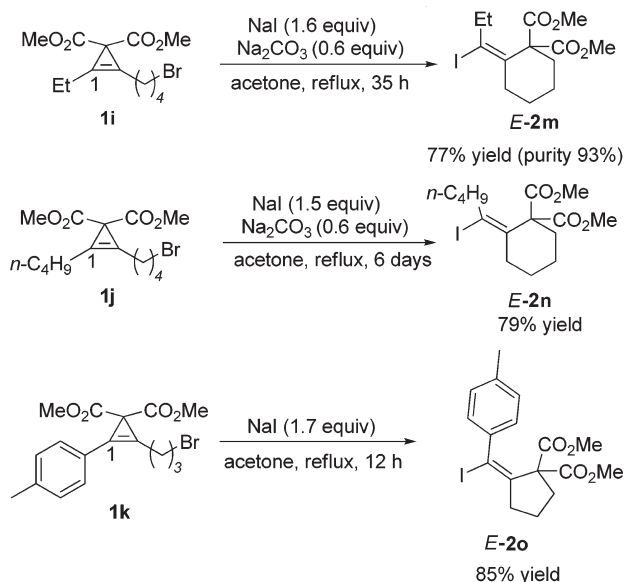
(12) Crystal data for compound **E-2a**: C₁₆H₁₇O₄I, MW = 400.20, monoclinic, space group *P2(1)/c*, final *R* indices [*I* > 2σ(*I*)], *R*₁ = 0.0332, *wR*₂ = 0.0847, *R* indices (all data), *R*₁ = 0.0394, *wR*₂ = 0.0878, *a* = 9.1568 (7) Å, *b* = 19.9575 (16) Å, *c* = 9.6108 (7) Å, α = 90°, β = 114.2340(1)°, γ = 90°, *V* = 1601.6 (2) Å³, *T* = 293(2) K, *Z* = 4, reflections collected/unique: 9277/3483 (*R*(int) = 0.0446), number of observations [*I* > 2σ(*I*)] 2984, parameters 193. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 694977. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336- 033; E-mail: deposit@ccdc.cam.ac.uk).

(13) Crystal data for compound **E-2b**: C₁₂H₁₇O₄I, MW = 352.16, monoclinic, space group *P2(1)/c*, final *R* indices [*I* > 2σ(*I*)], *R*₁ = 0.0416, *wR*₂ = 0.1048, *R* indices (all data), *R*₁ = 0.0460, *wR*₂ = 0.1075, *a* = 8.2163(9) Å, *b* = 13.1526(15) Å, *c* = 12.5835(14) Å, α = 90°, β = 95.994(2)°, γ = 90°, *V* = 1352.4 (3) Å³, *T* = 293(2) K, *Z* = 4, reflections collected/unique: 7777/2944 (*R*(int) = 0.0900), number of observations [*I* > 2σ(*I*)] 2565, parameters 157. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 694978. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336- 033; E-mail: deposit@ccdc.cam.ac.uk).

TABLE 3. Scope of the Ring-Opening Cyclization Reaction

entry	R ¹	R ²	m	MX ^a	time (h)	yield of 2 ^{b,c} (%)
1	CO ₂ Me	CO ₂ Me	3 (1c)	A	0.8	81 (61) (<i>E</i> -2c) ^d
2	CO ₂ Me	CO ₂ Me	3 (1c)	B	2.7	96 (86) (<i>E</i> -2d)
3	CH ₃ CO	CO ₂ Et	3 (1d)	A	0.5	82 (65) (<i>E</i> -2e)
4	CH ₃ CO	CO ₂ Et	3 (1d)	B	1	84 (87) (<i>E</i> -2f)
5	CH ₃ CO	SO ₂ Ph	3 (1e)	A	3	76 (92) (<i>E</i> -2g)
6	CH ₃ CO	SO ₂ Ph	3 (1e)	B	3	77 (85) (<i>E</i> -2h)
7	CO ₂ Me	SO ₂ Ph	3 (1f)	A	4	79 (75) (<i>E</i> -2i)
8	CO ₂ Me	SO ₂ Ph	3 (1f)	B	16	71 (81) (<i>E</i> -2j) ^e
9	CO ₂ Me	CO ₂ Me	4 (1g)	A	1	69 (76) (<i>E</i> -2k) ^f
10	CO ₂ Me	CO ₂ Me	2 (1h)	A	10	22 (27) (<i>E</i> -2l)

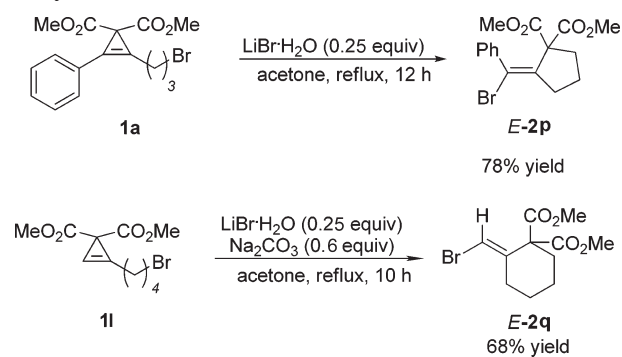
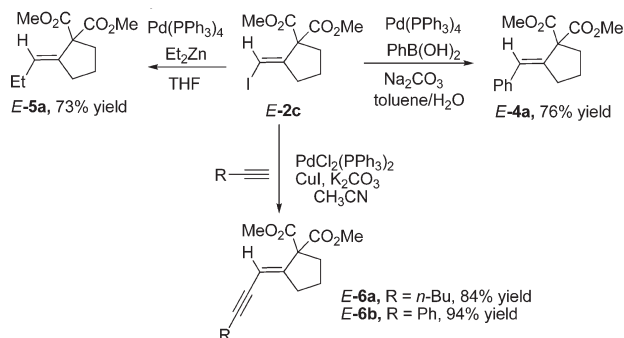
^aA = NaI, B = LiBr·H₂O. ^bIsolated yield. ^cThe numbers in parentheses are isolated yields for the reactions carried out in the absence of Na₂CO₃. ^d2.4 equiv of NaI were used. ^e2.4 equiv of LiBr·H₂O were used. ^fWhen **1l** was applied to the reaction with 0.6 equiv of Na₂CO₃ as the additive, the yield of *E*-2k was 78%.

SCHEME 1. The Reactions of Cyclopropenes **1i**, **1j**, and **1k** with NaI

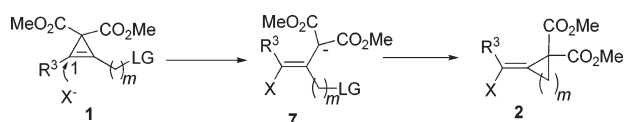
As expected, the reactions of **1a** and **1l** with LiBr·H₂O occurred smoothly with only a catalytic amount of LiBr·H₂O (Scheme 2).

The synthetic utilities of the product *E*-2 were demonstrated by the transformation of the representative product *E*-2c (Scheme 3). Treatment of *E*-2c with phenyl boronic acid or diethyl zinc gave the coupling products *E*-4a and *E*-5a in 76% and 73% yields, respectively. Phenylacetylene and 1-hexyne underwent the Sonogashira coupling reaction with *E*-2c to afford stereodefined conjugated enynes *E*-6a and *E*-6b in excellent yields.

The plausible mechanism for this transformation is depicted in Scheme 4. The nucleophile X⁻ (I⁻ and Br⁻)

SCHEME 2. The Reactions of Cyclopropenes **1a** and **1l** with a Catalytic Amount of LiBr·H₂OSCHEME 3. The Synthetic Utilities of the Product *E*-2c

SCHEME 4. The Plausible Mechanism for the Ring-Opening Cyclization Reaction



attacked regioselectively the sp² carbon atom at the 1-position of cyclopropenes **1** to give a stereodefined carbanion **7**, which would undergo intramolecular nucleophilic substitutions to afford *E*-2.

In conclusion, we have developed an X⁻ (X = I, Br)-triggered ring-opening intramolecular trapping of cyclopropenyl-substituted alkyl bromides or mesylates providing an efficient highly regio- and stereoselective approach to the synthesis of (*E*)-haloalkylidene cyclic compounds. Further studies on the scope of the reaction and the synthetic application are now being carried out in our laboratory.

Experimental Section

General Procedure for the Ring-Opening Cyclization Reaction. To a reaction tube were added sequentially NaI (35 mg, 0.23 mmol), 1.5 mL of acetone, **1a** (54 mg, 0.15 mmol), and 1.5 mL of acetone. The resulting mixture was refluxed for 2 days as monitored by TLC. Evaporation and column chromatography on silica gel (eluent: petroleum ether/Et₂O = 10/1) afforded *E*-2a¹⁴ (49 mg, 80%): solid,

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m.p. 90–91 °C (petroleum ether/ethyl acetate); ^1H NMR (300 MHz, CDCl_3) δ 7.35–7.30 (m, 2H), 7.27–7.13 (m, 3H), 3.38 (s, 6H), 2.67 (t, $J = 7.5$ Hz, 2H), 2.55 (t, $J = 6.9$ Hz, 2H), 1.78–1.65 (m, 2H); ^{13}C NMR (75.4 MHz, CDCl_3) δ 170.0, 146.2, 142.9, 128.8, 127.9, 127.6, 98.2, 64.9, 52.5, 42.7, 40.9, 22.8; MS (ESI) m/z 455 ($\text{M} + \text{CH}_3\text{OH} + \text{Na}^+$), 423 ($\text{M} + \text{Na}^+$), 401 ($\text{M} + \text{H}^+$); IR (KBr) 2951, 1731, 1433, 1267 cm^{-1} . Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{O}_4\text{I}$: C 48.02; H 4.28. Found: C 48.22; H 4.51.

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Supporting Information Available: Experimental procedures, characterization of the products, and the CIF files of *E-2a* and *E-2b*. This material is available free of charge via the Internet at <http://pubs.acs.org>.