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Addition of hydrogen halides to alkylidenecyclopropanes: a highly efficient and stereoselective method for the preparation of homoallylic halides

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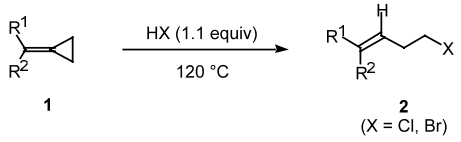
Abstract—The reaction of alkylidenecyclopropanes with HCl or with HBr proceeds very smoothly at 120°C to produce the corresponding homoallylic halides stereoselectively in good to excellent yields. For example, the reaction of (1-phenylbenzylidene)cyclopropane, (1-butylpentylidene)cyclopropane and octylidenecyclopropane with hydrochloric acid produced the corresponding homoallylic chlorides, 4-chloro-1,1-diphenyl-1-butene, 4-butyl-1-chloro-3-octene and (*E*)-1-chloro-3-undecene in 99, 96, and 87% yields, respectively. The reaction of (1-butylpentylidene)cyclopropane with hydrobromic acid yielded 1-bromo-4-butyl-3-octene in 95% yield.

Homoallylic halides have attracted considerable attention because of their versatility as a building block or starting substrate in organic synthesis[1] and in the pharmaceutical and agrochemical industries.[2a] However, the synthesis of homoallylic halides is limited by the lack of a general synthetic route. Previously described methodologies are generally not widely applicable due to limited scope,[2a] low yields,[2a] difficult workup procedures,[2a–d] and high cost.[3] Especially, *the stereoselective synthesis of unsymmetrical gem-disubstituted* ($R^1 \neq R^2$) homoallylic halides is not easy. During the last decade, methylenecyclopropanes (MCPs) have become readily available and found application in organic synthesis as versatile building blocks. Their chemical reactivity is due to a high level of ring strain, although they are surprisingly stable and easy to handle.[4] A long time ago, Köster et al. and Donskaya et al. reported addition of hydrogen halides to methylencyclopanes.[5] However, these reactions were limited in scope, low yielding, and not selective. We report a convenient, efficient and stereoselective procedure for the synthesis of homoallylic halides; the reaction of hydrogen halides with MCPs **1** in 1,4-dioxane (HCl) or in HOAc (HBr) at 120°C gives the corresponding homoallylic halides **2** in good to excellent yields (Eq. (1)).



1 **2** (X = Cl, Br) (1)

The results are summarized in Table 1. The symmetrical MCPs, (1-phenylbenzylidene)cyclopropane **1a**, (1-butylpentylidene)cyclopropane **1b** and (1-hexylheptylidene)cyclopropane **1c**, underwent facile ring-opening of the cyclopropane ring at 120°C with 4 M hydrogen chloride in 1,4-dioxane to afford **2a**, **2b** and **2c** in 99%, 96% and 94% yield, respectively (entries 1, 2 and 3). Interestingly, the reaction of **1b** with 1 M hydrogen chloride in ether at 120°C produced the corresponding homoallylic chloride **2b** in 95% yield (entry 2).[6] All reactions were very rapid and completed within 10 min. At lower temperatures (60–100°C), longer reaction times were needed and the products were obtained in lower yields. Similarly, (dicyclohexylmethylene)cyclopropane **1d** gave the corresponding homoallylic chloride **2d** in 89% yield (entry 4). Likewise, the addition of hydrogen chloride to an unsymmetrical MCP, (3-cyclopropylidenemethyl)cyclohexane **1e** proceeded smoothly to afford stereoselectively the *E*-homoallylic chloride **2e** (entry 5). Furthermore, the reaction with HCl of octylidenecyclopropane **1f** and (3-cyclopropylidenepropyl)benzene **1g** was completed within 10 min, producing **2f** and **2g** in 87 and 86% yield, respectively, with exclusive *E*-selectivity (entries 6 and 7). The reaction of ethyl 4-cyclopropylidenepentanoate **1h** bearing an electron-withdrawing functional group gave **2h** in

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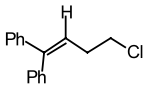
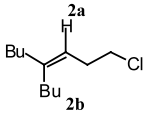
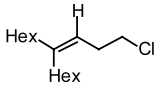
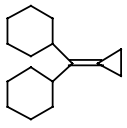
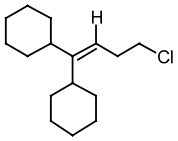
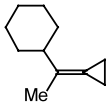
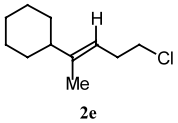
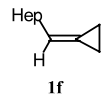
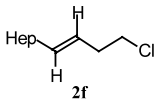
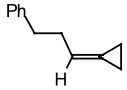
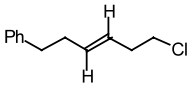
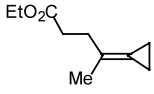
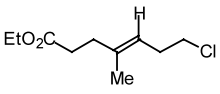
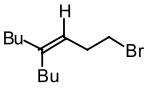
Table 1. Addition of hydrogen chloride and bromide to alkylidene-cyclopropanes **1**[a]

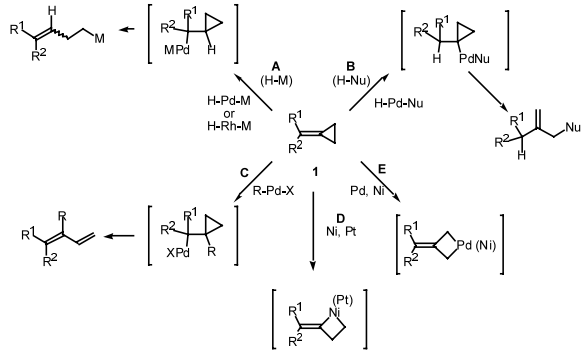
entry	1	2	yield / %[b]
1	 **1a**	 **2a**	99
2	 **1b**	 **2b**	96 (95)[c]
3	 **1c**	 **2c**	94
4	 **1d**	 **2d**	89
5	 **1e**	 **2e**	85
6	 **1f**	 **2f**	87
7	 **1g**	 **2g**	86
8	 **1h**	 **2h**	83
9	 **1b**	 **2i**	95

[a] The reaction of **1** (0.5 mmol) with 4 M hydrogen chloride in 1,4-dioxane (0.55 mmol) or 1 M hydrogen bromide in acetic acid (0.55 mmol) was carried out at 120°C. All reactions, which were carried out in a well sealed pressure vial, were monitored by GC for 10 min.

[b] Isolated yield based on **1**.

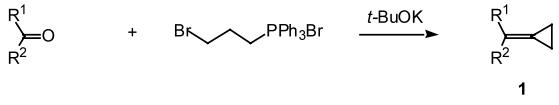
[c] Number in parentheses indicates the reaction of **1** with 1 M hydrogen chloride in ether.

good yield (entry 8). The *E*/*Z* selectivity was determined by the 500 MHz ^{1}H NMR spectra of the products **2e–h**. For further investigation of the potential of this reaction, the reaction of hydrogen bromide with the MCP **1b** was examined. The reaction of **1b** with 1 M hydrogen bromide in acetic acid gave the corresponding homoallylic bromide **2i** in 95% yield (entry 9).



Scheme 1.

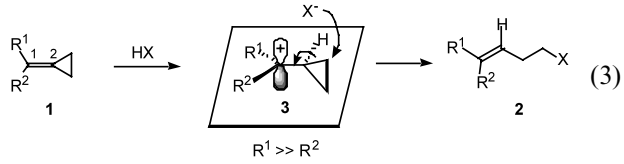
The substituted MCPs **1** are readily available by the reaction of aldehydes/ketones with 3-bromopropylphosphonium bromide (Eq. (2)).[7] It should be noted that we do not need to take care of the stereochemical problem at the stage of the preparation of **1** as perfect stereocontrol is accomplished during the addition of HX to **1**. It is worth considering why such high stereo- and regioselective ring opening of MCPs takes place with the simple reagents, HCl and HBr, since various reaction pathways have been revealed in the transition metal-catalyzed reactions of MCPs using H–M (hydrosilanes and hydrostannanes) and H–Nu (carbon and heteroatom pronucleophiles).[8]



(2)

The major pathways of the transition metal-catalyzed reactions are summarized in Scheme 1. The additions of H–M through H–Pd–M or H–Rh–M intermediates (route A), H–Nu through H–Pd–Nu (route B), and R–X through R–Pd–X intermediates (route C) take place at the C–C double bond of **1** although the regioselectivities of the addition depend on the substrate structure and/or the reactivity of the intermediates. In the absence of those substrates (H–M, H–Nu and R–X), the insertion of Pd(0), Ni(0), or Pt(0) either into the proximal or into the distal bond of cyclopropane ring takes place first (route D and E), and then the resulting metallacyclobutanes react with unsaturated bonds (X=Y)[8p–s] or with metal–metal bonds (for example B–Si).[8a] Accordingly, the transition metal-catalyzed addition of H–M occurs at the C–C double bond perhaps due to its higher electron density. The regioselective protonation with HCl or HBr must take place at the C-2 position of the double bond to produce the cyclopropylcarbinyl cation **3** (Eq. (3)).[9] The protonation at the C-1 position leads to a less stable cyclopropyl cation. If R^1 is sterically bulkier than R^2, the smallest group H is located most probably on the R^1 side of the plane as shown in **3** and the cyclopropyl group is on the R^2 side. The ring opening of the cyclopropyl group and concomitant bond migration would give **2** stereoselectively. Taken together, the simple protonation of **1** affords the stable cyclopropylcarbinyl cation intermediate **3** which controls the

subsequent stereoselective chemical process, while the transition metal-catalyzed H–M addition does not proceed through intervention of an ionic species but proceeds via rather neutral organometallic intermediates which do not possess the biased conformation observed in the cyclopropylcarbinyl cation, and therefore lead to diverse regio- and stereoselectivities.



(3)

To the best of our knowledge, the present reaction provides the most general, efficient and direct protocol for the stereoselective preparation of *gem*-disubstituted homoallylic halides; it was rather surprising to us why such a simple reaction has not been found until now. In addition to the practical usefulness of the reaction, it is interesting to compare the mechanisms of the modern transition metal-catalyzed reactions with a classical organic reaction.

General experimental procedure of the addition of hydrogen chloride to the alkylidenecyclopropane 1b. To the alkylidenecyclopropane **1b** (83.1 mg, 0.5 mmol) was added 4 M hydrogen chloride in dioxane (0.14 mL, 0.55 mmol) under Ar atmosphere in a pressure vial and the mixture was stirred at 120°C for 10 min. After completion of the reaction, which was monitored by GC, the mixture was filtered through a short silica column with ethyl acetate as eluent. Purification of the crude product with silica column chromatography (hexane as eluent) afforded the homoallylic chloride **2b** in 96% yield.

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